

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification : C12N 15/62, C07K 19/00, C12N 1/21, 5/10, C12Q 1/37, 1/533 // C07K 14/18, C12N 9/50	A2	(11) International Publication Number: WO 99/28482 (43) International Publication Date: 10 June 1999 (10.06.99)
(21) International Application Number: PCT/US98/24528 (22) International Filing Date: 24 November 1998 (24.11.98) (30) Priority Data: 60/067,315 28 November 1997 (28.11.97): US 60/094,331 28 July 1998 (28.07.98) US (71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US). (72) Inventors: MALCOLM, Bruce, A.; 515 Trinity Place, Westfield, NJ 07090 (US). TAREMI, S., Shane; 12 Park Terrace, Upper Montclair, NJ 07043 (US). WEBER, Patricia, C.; 1970 Timber Lakes Drive, Yardley, PA 19067 (US). YAO, Nanhua; 4 Timothy Court, Edison, NJ 08837 (US). (74) Agents: McLAUGHLIN, Jaye, P. et al.; Schering-Plough Corporation, Patent Dept., K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GD, GE, HR, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: SINGLE-CHAIN RECOMBINANT COMPLEXES OF HEPATITIS C VIRUS NS3 PROTEASE AND NS4A COFACTOR PEPTIDE (57) Abstract Covalent HCV NS4A-NS3 complexes comprising the central hydrophobic domain of native HCV NS4A peptide, a linker, and the HCV NS3 serine protease domain, wherein the hydrophobic domain of native HCV NS4A peptide is tethered by the linker to the amino terminus of the HCV NS3 protease domain.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

**SINGLE-CHAIN RECOMBINANT COMPLEXES OF HEPATITIS C
VIRUS NS3 PROTEASE AND NS4A COFACTOR PEPTIDE**

5 This filing claims priority from Provisional U.S. Patent Applications USSN 60/067,315, filed November 28, 1997 and USSN 60/094,331, filed July 28, 1998, each of which is incorporated herein by reference.

10 **BACKGROUND OF THE INVENTION**

Hepatitis C virus (HCV) is considered to be the major etiological agent of non-A non-B (NANB) hepatitis, chronic liver disease, and
15 hepatocellular carcinoma (HCC) around the world, with an estimated human seroprevalence of 1% globally. [Alter *et al.*, 1994, *Gastroenterol. Clin. North Am.* 23:437-455; Behrens *et al.*, 1996, *EMBO J.* 15:12-22]. Four million individuals may be infected in the United States. The viral infection accounts for greater than 90% of transfusion-associated
20 hepatitis in the U.S. and it is the predominant form of hepatitis in adults over 40 years of age. Almost all of the infections result in chronic hepatitis and nearly 20% of those infected develop liver cirrhosis.

The virus particle has not been identified due to the lack of an efficient *ex vivo* replication system and the extremely low amount of
25 HCV particles in infected liver tissues or blood. However, molecular cloning of the viral genome has been accomplished by isolating the messenger RNA (mRNA) from the serum of infected chimpanzees and preparing cDNA using recombinant methodologies. [Grakoui A. *et al.*, 1993, *J. Virol.* 67: 1385-1395]. It is now known that HCV contains a
30 positive strand RNA genome comprising approximately 9400 nucleotides, organization of which is similar to that of flaviviruses and pestiviruses. The genome of HCV, a (+)-stranded RNA molecule of ~9.4 kb, encodes a single large polyprotein of about 3000 amino acids which undergoes proteolysis to form mature viral proteins in infected cells.

- 2 -

Cell-free translation of the viral polyprotein and cell culture expression studies have established that the HCV polyprotein is processed by cellular and viral proteases to produce the putative structural and nonstructural (NS) proteins. At least ten mature viral proteins are produced from the polyprotein by specific proteolysis. The order and nomenclature of the cleavage products are as follows: NH₂-C-E1-E2-p7-NS2-NS4A-NS3-NS4B-NS5A-NS5B-COOH (Fig. 1) [Grakoui *et al.*, 1993, *J. Virol.* 67:1385-95; Hijikata *et al.*, 1991, *PNAS* 88:5547-51; Lin *et al.*, 1994, *J. Virol.* 68:5063-73]. The three amino-terminal putative structural proteins, C (capsid), E1, and E2 (two envelope glycoproteins), are believed to be cleaved by a host signal peptidase of the endoplasmic reticulum (ER). The host enzyme is also responsible for generating the amino terminus of NS2. The proteolytic processing of the nonstructural proteins are carried out by the viral proteases: NS2-3 and NS3, contained within the viral polyprotein. The NS2-3 protease catalyzes the cleavage between NS2 and NS3. It is a metalloprotease and requires both NS2 and the protease domain of NS3.

The NS3 protease catalyzes the rest of the cleavages in the nonstructural part of the polyprotein. The NS3 protein contains 631 amino acid residues and is comprised of two enzymatic activities: the protease domain contained within amino acid residues 1-181 and a helicase ATPase domain contained within the rest of the protein Kim *et al.*, 1995, *Biochem Biophys Res. Comm.*, 215:160-166. It is not known if the 70 kD NS3 protein is cleaved further in infected cells to separate the protease domain from the helicase domain, although no cleavage has been observed in cell culture expression studies.

The NS3 protease is a member of the serine class of enzymes. It uses a His, Asp, Ser catalytic triad. Mutation of the Ser residue abolishes cleavage of NS3/4A, NS4A/4B, NS4B/5A, and NS5A/5B substrates. The cleavage between NS3 and NS4A is intramolecular, whereas the cleavages at the NS 4A/4B, 4B/5A, 5A/5B sites occur in *trans*.

- 3 -

Experiments using transient expression of various forms of HCV NS polyproteins in mammalian cells have established that the NS3 serine protease is necessary but not sufficient for efficient processing of all of these cleavages. Like the flaviviruses, the HCV NS3 protease also requires a cofactor to catalyze some of these cleavage reactions. Efficient proteolytic processing at NS3/4A, NS4A/4B, NS4B/5A, and NS5A/5B sites within the non-structural domain of hepatitis C virus requires a heterodimeric complex of the NS3 serine protease and the NS4A protein. [Bartenschlager *et al.* 1995, *J. Virol.* 67:3835-3844; Failla *et al.*, 1994, *J. Virol.* 68:3753-3760]. A 13-amino acid synthetic NS4A peptide, corresponding to the central hydrophobic domain of NS4A protein, spanning residues 21-33 has been shown to be sufficient for activation of NS3 protease [Butkiewicz *et al.*, 1996, *Virology*, 225: 328-338]. A smaller domain (amino acid residues 22-30) of NS4A has been shown to be sufficient for activation of the protease [Lin *et al.*, 1995, *J. Virol* 69:4377-80].

The recently published three dimensional structure of the NS3 protease [Kim *et al.*, 1996, *Cell* 87:343-355; Love *et al.*, 1996, *Cell* 87:331-342] revealed that the N-terminal 37 residues of NS3 adopt a β (residues 6-9)- α (residues 14-22)- β (residues 33-37) structure upon binding of a synthetic peptide corresponding to the central hydrophobic domain spanning residues 21-32 of NS4A protein.

Production of an active NS3₁₋₁₈₁-NS4A peptide complex at present involves two steps. First, the NS3 catalytic domain (amino acid residues 1-181) is produced as a recombinant protein in *E. coli*. Next, a 13-19 residue NS4A peptide spanning the central hydrophobic domain of the full-length NS4A protein is added to form a non-covalent complex [Kim *et al.*, 1996, *Cell* 87:343-355]. This complex, although more active than the protease alone, is approximately 8-10 fold less active than the full-length NS3₁₋₆₃₁-NS4A₁₋₅₄ form of the protease as judged by its proteolytic activity toward a synthetic substrate based on the native NS5A-NS5B amino acid sequence. [Urbani *et al.*, 1997, *J. Biol. Chem.*,

- 4 -

272(14):9204-09; Steinkuhler *et al.*, 1996, *J. Virol.* 70(10):6694-6700].

Moreover, NS4A peptide has been shown to have a very low affinity (10 μ M) for NS3 in solution [Bianchi *et al.*, 1997, *Biochemistry* 36: 7890-7897], requiring addition of NS4A peptide in the high micromolar range to
5 insure a 1:1 stoichiometric complex with NS3 protease. The limited solubility of this peptide in aqueous buffer due to its hydrophobic nature makes working with this peptide at these concentrations difficult.

Because the HCV NS3 protease cleaves the non-structural HCV proteins necessary for HCV replication, the NS3 protease can be a target
10 for the development of therapeutic agents against the HCV virus. The gene encoding the HCV NS3 protein has been cloned as disclosed in U.S. Patent No. 5,371,017. To date, however, the protease has not been produced in a covalent complex with the NS4A cofactor in a soluble, active and stable form. Such a complex would be useful as a target in a
15 high throughput screen to discover therapeutic agents. A stable, active HCV protease is also required for determination of modes of binding of inhibitors by NMR, for structural determination by NMR spectroscopy, for crystallography, and for virtually all biophysical and biochemical studies interested in the activated form of the enzyme.

SUMMARY OF THE INVENTION

The present invention provides NS4A tethered forms of the HCV
25 NS3 protease comprising single-chain recombinant covalent complexes of Hepatitis C virus NS3 protease and an NS4A cofactor peptide which require no subsequent addition of NS4A peptide for activation and which are as active as the full-length NS3₁₋₆₃₁ NS4A₁₋₅₄. The covalent NS4A-NS3 complexes of the invention are more soluble, stable and
30 active than the non-covalent protease-peptide complexes previously available.

The NS4A tethered forms of the HCV NS3 protease of the invention consist of covalent NS4A-NS3 complexes comprising a

- 5 -

central hydrophobic domain of the NS4A peptide tethered by linker of at least about 4 amino acid residues to the amino terminus of the serine protease domain of NS3. The amino acid sequences of 20 such

embodiments are defined in the Sequence Listing by SEQ ID NOs: 1-20.
5 Corresponding nucleotide sequences are provided in SEQ ID NOs: 91-111.

Preferred embodiments of the invention also provide NS4A tethered forms of the full length NS3 protease. The amino acid sequences of 8 such embodiments are defined in SEQ ID NOs: 11-18.

10 Other preferred embodiments of the invention further provide mutant forms of the covalent NS4A-NS3 complexes in which point mutations introduced at positions 17 and/or 18 of the NS3 domain change a hydrophobic amino acid residue to a hydrophilic residue. This further improves the solubility of the complexes and provides the
15 protein in a monodispersed form. The amino acid sequences of 13 such embodiments are defined in the Sequence Listing by SEQ ID NOs: 2-4, 6-8, 10, 12-14, and 16-18.

The invention still further provides mutant forms of the covalent NS4A-NS3 complexes in which a mutation introduced at position 139 of
20 the NS3 domain changes a serine residue to an alanine residue. The amino acid sequences of 9 such embodiments are defined in SEQ ID NOs: 5-8, 15-18 and 20.

The invention further provides covalent HCV NS4A-NS3 complexes having an easily removable histidine tag comprising three or
25 more histidine residues fused to the complex. This enables rapid purification of the protease with easy removal of the tag following purification.

The present invention further provides for isolated nucleic acids and vectors which encode the covalent NS4A-NS3 complexes of the
30 present invention, and host cells transformed or transfected by said nucleic acids or vectors.

- 6 -

The invention still further provides methods for making the covalent NS4A-NS3 complexes comprising culturing the transformed or transfected host cell under conditions in which the nucleic acid or vector is expressed.

5 The invention also provides methods for identifying inhibitors of HCV NS3. Methods are provided for detecting inhibitors of the protease activity, the helicase activity and the ATPase activity of NS3 using the disclosed covalent complexes.

10

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 schematically depicts the HCV genome.

15 Figure 2 depicts the recombinant synthesis of plasmid pHIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁.

Figure 3 depicts the recombinant synthesis of plasmid pHIS-NS3₁₋₆₃₁.

20 Figure 4 depicts the recombinant synthesis of plasmid pHIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁.

Figures 5A and 5B schematically depict a high throughput assay for discovering HCV protease inhibitors using surface plasmon resonance technology. Figure 5A illustrates the outcome expected in the absence of
25 an uninhibited HCV protease, while 5B illustrates the outcome expected in the presence of an active, uninhibited HCV protease.

Figure 6 shows the nucleic acid unwinding activity of the covalent His-
30 NS4A₂₁₋₃₂-GSGS-NS₃₃₋₆₃₁ as compared to that of the His NS3₁₋₆₃₁/NS4A₁₋₅₄

Figure 7 shows the ATPase activity of the covalent His-NS4A₂₁₋₃₂-GSGS-NS₃₃₋₆₃₁ complex as monitored by thin layer chromatography.

DETAILED DESCRIPTION OF THE INVENTION

5 The teachings of all references cited are incorporated herein in their entirety by reference.

 The covalent NS4A-NS3 complexes of the present invention are useful for structural determination and determination of mode of binding of HCV inhibitors by NMR spectroscopy. Moreover, they
10 provide a more soluble and stable form of HCV NS3 protease than the presently available non-covalent NS3₁₋₁₈₁-NS4A peptide complexes for crystallography studies, high throughput screening assays and other conventional biophysical and biochemical investigations.

 Several representative embodiments of the covalent NS4A-NS3
15 complexes of the invention are disclosed in the examples below. In one such embodiment, NS4A residues 21-32 were tethered to the amino terminus of residues 3-181 of mature NS3 protease by a 4-residue linker, GSGS (SEQ ID NO: 21). The complex was overexpressed as a soluble
20 protein in *E. coli* and purified to homogeneity by a combination of metal chelate and size-exclusion chromatography. The tethered complex, HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁ (SEQ ID NO: 1) cleaved a NS5A/5B synthetic substrate with a catalytic efficiency identical to that of the non-covalent full-length protease, NS3₁₋₆₃₁-NS4A₁₋₅₄.

 In other embodiments of the invention, the NS4A hydrophobic
25 domain and the NS3 serine protease domain are covalently tethered using different amino acid linkers. The preferred amino acid linkers of the invention comprise at least about four amino acid residues. More preferably, the linkers consist of from four to six amino acid residues. More preferably, four-residue linkers are used. Most preferably, amino
30 acid linkers having the sequence defined by SEQ ID NO: 21 or 22 are used to tether the NS4A hydrophobic domain and the NS3 serine protease domain.

 Routine procedures in the art would allow one to construct covalent NS4A-NS3 complexes of the invention having linkers of

various sizes. It will be understood by one skilled in the art, for example, that if smaller or larger portions of the NS3 or NS4A domains are used to construct the covalent complexes of the invention, longer or shorter amino acid linkers can be used.

5 Other embodiments of the present invention contain smaller or larger portions of the NS4A cofactor peptide. In preferred embodiments, the complexes contain an NS4A hydrophobic domain comprising at least amino acid residues 22-30 of the full length NS4A cofactor peptide. More preferably, the complexes contain from 12-19 amino acid residues
10 spanning the central hydrophobic domain of the full length NS4A peptide. Most preferably, the complexes contain amino acid residues 21-32 of full length NS4A peptide.

Still further embodiments of the present invention contain smaller or larger portions of the NS3 protease. In preferred
15 embodiments, the complexes contain an NS3 serine protease domain comprising at least amino acid residues 3-181 of the full length NS3 protease. More preferably, the complexes contain amino acid residues 1-181 of full length NS3 protease. Most preferably, the complexes contain amino acid residues 3-181 of full length NS3 protease.

20 The present invention thus also includes covalent NS4A-NS3 complexes comprising the central hydrophobic domain of the NS4A peptide tethered to the amino terminus of full-length mature NS3 protease (amino acids 1-631) by an amino acid linker. The amino acid sequences of preferred embodiments comprising NS4A tethered to full-
25 length mature NS3 protease are set forth in SEQ ID NOs: 11-18.

Surprisingly, it has also been found that the introduction of point mutations at position 17 and/or 18 of the NS3 domain of the NS4A- NS3 constructs of the present invention which change a hydrophobic amino acid residue to a hydrophilic amino acid residue produces a more soluble
30 and mono-dispersed form of the tethered complex. Thirteen representative embodiments of such mutant NS4A-NS3 complexes are disclosed in the Examples below. In some embodiments, the isoleucine

- 9 -

at position 17 is mutated to lysine. One such mutant form is referred to as His-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/I17K (SEQ ID NO: 2). In other embodiments, the same mutation is made at position 18. One such mutant form is referred to as His-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/I18K (SEQ ID NO: 3). In yet other embodiments, the mutations are introduced at both positions. One such mutant is referred to as His-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/I17K,I18K (SEQ ID NO: 4). Each of the purified mutants results in a monodispersed (as judged by size exclusion chromatography) and more soluble (as judged by achieving higher concentration of the complex 17-20 mg/ml) form of the complex, which remains monodispersed for a period of about one week at 4°C, while still exhibiting kinetic properties identical to those of the wild type.

It will be understood that although the foregoing embodiments are presently preferred, other modifications to the hydrophobic residues at positions 17 and 18 can be made to produce other soluble complexes. Preferably, neutral amino acid residues will be substituted for charged residues. These modifications can be used in a number of combinations to produce the final modified protein chain.

Also provided are NS4A-tethered forms of NS3 full-length domain. In contrast to the NS4A-tethered forms of the catalytic domain, a considerable amount of autocleavage in the helicase domain of the NS3 protein is detected during the purification of their native full-length counterpart, HIS-NS4A₂₁₋₃₂-NS3₃₋₆₃₁. To prevent autocleavage of the full-length covalent complexes, the catalytic serine residue at position 139 is mutated to alanine. The amino acid sequence of one such embodiment is defined by SEQ ID NO: 15. The mutation of the full length constructs at position 139 can also be made in the NS4A-tethered forms of the NS3 catalytic domain, and can be made in combination with any of the aforementioned mutations to increase solubility and stability while preventing autocleavage. Representative embodiments are set forth in SEQ ID NOs: 5-8, 15-18 and 20.

- 10 -

As used herein, the terms "native NS3" and "full-length NS3" are used interchangeably and are defined as a protein which (a) has an amino acid sequence substantially identical to the sequence defined by SEQ ID NO: 23 and (b) has biological activity that is common to native NS3. This includes natural allelic variants and other variants having one or more conservative amino acid substitutions [Grantham, 1974, *Science* 185:862] that do not substantially impair biological activity. Such conservative substitutions involve groups of synonymous amino acids, e.g., as described in U.S. patent No. 5,017,691 to Lee *et al.*

The "serine protease domain" of NS3 or the "catalytic domain" of NS3 refers to amino acids 1-181 of mature NS3, which have been shown to contain the active catalytic triad His, Asp and Ser.

The term "native NS4A peptide" as used herein is defined as a peptide which (a) has an amino acid sequence substantially identical to the sequence defined by SEQ ID NO: 24; and (b) has biological activity that is common to native NS4A. This includes natural allelic variants and other variants having one or more conservative amino acid substitution [Grantham, 1974, *Science* 185:862] that do not substantially impair biological activity. Such conservative substitutions involve groups of synonymous amino acids, e.g., as described in U.S. patent No. 5,017,691 to Lee *et al.*

As used herein, the "central hydrophobic domain of NS4A peptide" refers to that portion of the native NS4A peptide (approximately amino acid residues 22 - 30) which is sufficient for activation of NS3 protease. Size and sequence variants of this domain which also activate the NS3 protease in the claimed complexes also fall within this term.

A "soluble" covalent complex as referred to herein is defined as a protein which will remain in solution after a high spin centrifugation step at 300,000 x g in a standard ultracentrifuge in a buffer containing 25 mM HEPES, pH 7.6, 10% glycerol, 0.3 M NaCl, 10 mM β ME.

- 11 -

An "active" covalent complex as referred to herein is defined as a complex which will cleave synthetic substrates corresponding to NS5A-NS5B cleavage site (for example, DTEDVVCC SMYTWGK) (SEQ ID NO: 25)) between P1 residue, cysteine and P1' residue, serine in a buffer
5 containing 25 mM Tris, pH 7.5, 150 mM NaCl, 10 % glycerol, and 0.05 % lauryl maltoside.

Nucleic acids encoding the covalent NS4A-NS3 complexes are also a part of this invention. DNA encoding the covalent NS4A-NS3 complexes of this invention can be prepared by chemical synthesis
10 using the known nucleic acid sequence [Ratner *et al.*, 1985, *Nucleic Acids Res.* 13:5007] and standard methods such as the phosphoramidite solid support method of Matteucci *et al.*, 1981, *J. Am. Chem. Soc.* 103:3185 or the method of Yoo *et al.*, 1989, *J. Biol. Chem.* 764:17078. See also Glick, Bernard R. and Pasternak, *Molecular*
15 *Biotechnology*, pages 55 - 63, (ASM Press, Washington, D.C. 1994). The genes encoding the desired regions of the HCV protein can also be obtained using the plasmid disclosed in Grakoui, *et al.*, 1993, *J. Virol.* 67:1385-1395 or that disclosed in Takamizawa *et al.*, 1991, *J. Virology* 65(3):1105-1113. Also, the nucleic acid encoding HCV NS3
20 and NS4A can be isolated, amplified and cloned from patients infected with the HCV virus. Furthermore, the HCV genome has been disclosed in PCT WO 89/04669 and is available from the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, MD under ATCC accession no. 40394.

25 Of course, because of the degeneracy of the genetic code, there are many functionally equivalent nucleic acid sequences that can encode the NS3 and NS4A domains of the covalent NS4A-NS3 complexes as defined herein. Such functionally equivalent sequences, which can readily be prepared using known methods such
30 as chemical synthesis, PCR employing modified primers and site-directed mutagenesis, are within the scope of this invention.

- 12 -

Various vectors can be used to express DNA encoding the covalent NS4A-NS3 complexes. Conventional vectors used for expression of recombinant proteins in prokaryotic or eukaryotic cells may be used. Preferred vectors include the pET vectors described by Studier *et al.*, 1990, *Methods of Enzymology* 185: 60-89, and the pcD vectors described by Okayama *et al.*, 1983, *Mol. Cell. Bio.* 3: 280-289; and Takebe *et al.*, 1988, *Mol. Cell. Biol.* 8: 466-472. Other SV40-based mammalian expression vectors include those disclosed in Kaufman *et al.*, 1982, *Mol. Cell. Biol.* 2: 1304-1319 and U.S. Patent No. 4,675,285. These SV40-based vectors are particularly useful in COS7 monkey cells (ATCC No. CRL 1651), as well as in other mammalian cells such as mouse L cells and CHO cells.

Standard transfection methods can be used to produce eukaryotic cell lines which express large quantities of polypeptides. Eukaryotic cell lines include mammalian, yeast and insect cell lines. Exemplary mammalian cell lines include COS-7 cells, mouse L cells and Chinese Hamster Ovary (CHO) cells. See Sambrook *et al.*, *supra* and Ausubel *et al.*, *supra*.

As used herein, the term "transformed bacteria" means bacteria that have been genetically engineered to produce a viral or mammalian protein. Such genetic engineering usually entails the introduction of an expression vector into a bacterium. The expression vector is capable of autonomous replication and protein expression relative to genes in the bacterial genome. Construction of bacterial expression vectors is well known in the art, provided the nucleotide sequence encoding a desired protein is known or otherwise ascertainable. For example, DeBoer in U.S. Pat. No. 4,551,433 discloses promoters for use in bacterial expression vectors; Goeddel *et al.* in U.S. Pat. No. 4,601,980 and Riggs, in U.S. Pat. No. 4,431,739 disclose the production of mammalian proteins by *E. coli* expression systems; and Riggs *supra*, Ferretti *et al.*, 1986, *Proc. Natl. Acad. Sci.* 83:599, Sproat *et al.*, 1985, *Nucleic Acid Research* 13:2959 and Mullenbach *et al.*, 1986, *J. Biol. Chem* 261:719 disclose how to construct

- 13 -

synthetic genes for expression in bacteria. Many bacterial expression vectors are available commercially and through the American Type Culture Collection (ATCC), Rockville, Maryland.

Insertion of DNA encoding the covalent NS4A-NS3 complexes
5 into a vector is easily accomplished when the termini of both the
DNA and the vector comprise the same restriction site. If this is not
the case, it may be necessary to modify the termini of the DNA
and/or vector by digesting back single-stranded DNA overhangs
generated by restriction endonuclease cleavage to produce blunt ends,
10 or to achieve the same result by filling in the single-stranded termini
with an appropriate DNA polymerase.

Alternatively, any site desired may be produced by ligating
nucleotide sequences (linkers) onto the termini. Such linkers may
comprise specific oligonucleotide sequences that define desired
15 restriction sites. The cleaved vector and the DNA fragments may
also be modified if required by homopolymeric tailing.

Many *E. coli*-compatible expression vectors can be used to
produce soluble covalent NS4A-NS3 complexes of the present
invention, including but not limited to vectors containing bacterial
20 or bacteriophage promoters such as the *Tac*, *Lac*, *Trp*, *LacUV5*, λ P_r
and λ P_L promoters. Preferably, a vector selected will have expression
control sequences that permit regulation of the rate of expression.
Then, production of covalent NS4A-NS3 complexes can be regulated
to avoid overproduction that could prove toxic to the host cells.
25 Most preferred is a vector comprising, from 5' to 3' (upstream to
downstream), a *Tac* promoter, a *lac* I^q repressor gene and DNA
encoding mature human HCV protease. The vectors chosen for use
in this invention may also encode secretory leaders such as the
ompA or protein A leader, as long as such leaders are cleaved during
30 post-translational processing to produce covalent NS4A-NS3

- 14 -

complexes or if the leaders are not cleaved, the leaders do not interfere with the enzymatic activity of the protease.

The covalent complexes of the invention, or portions thereof, can also be synthesized by a suitable method such as by exclusive solid phase synthesis, partial solid phase methods, fragment condensation or classical solution synthesis. The polypeptides are preferably prepared by solid phase peptide synthesis as described by Merrifield, 1963, *J. Am. Chem. Soc.* 85:2149. The synthesis is carried out with amino acids that are protected at the alpha-amino terminus. Trifunctional amino acids with labile side-chains are also protected with suitable groups to prevent undesired chemical reactions from occurring during the assembly of the polypeptides. The alpha-amino protecting group is selectively removed to allow subsequent reaction to take place at the amino-terminus. The conditions for the removal of the alpha-amino protecting group do not remove the side-chain protecting groups.

The alpha-amino protecting groups are those known to be useful in the art of stepwise polypeptide synthesis. Included are acyl type protecting groups (e.g., formyl, trifluoroacetyl, acetyl), aryl type protecting groups (e.g., biotinyl), aromatic urethane type protecting groups [e.g., benzyloxycarbonyl (Cbz), substituted benzyloxycarbonyl and 9-fluorenylmethyloxy-carbonyl (Fmoc)], aliphatic urethane protecting groups [e.g., t-butyloxycarbonyl (tBoc), isopropyloxycarbonyl, cyclohexyloxycarbonyl] and alkyl type protecting groups (e.g., benzyl, triphenylmethyl). The preferred protecting groups are tBoc and Fmoc, thus the peptides are said to be synthesized by tBoc and Fmoc chemistry, respectively.

The side-chain protecting groups selected must remain intact during coupling and not be removed during the deprotection of the amino-terminus protecting group or during coupling conditions. The side-chain protecting groups must also be removable upon the completion of synthesis, using reaction conditions that will not alter the finished polypeptide. In tBoc chemistry, the side-chain protecting

- 15 -

groups for trifunctional amino acids are mostly benzyl based. In Fmoc chemistry, they are mostly tert.-butyl or trityl based.

In tBoc chemistry, the preferred side-chain protecting groups are tosyl for Arg, cyclohexyl for Asp, 4-methylbenzyl (and acetamidomethyl) for Cys, benzyl for Glu, Ser and Thr, benzyloxymethyl (and dinitrophenyl) for His, 2-Cl-benzyloxycarbonyl for Lys, formyl for Trp and 2-bromobenzyl for Tyr. In Fmoc chemistry, the preferred side-chain protecting groups are 2,2,5,7,8-pentamethylchroman-6-sulfonyl (Pmc) or 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl (Pbf) for Arg, trityl for Asn, Cys, Gln and His, tert butyl for Asp, Glu, Ser, Thr and Tyr, tBoc for Lys and Trp.

For the synthesis of phosphopeptides, either direct or post-assembly incorporation of the phosphate group is used. In the direct incorporation strategy, the phosphate group on Ser, Thr or Tyr may be protected by methyl, benzyl or tert.butyl in Fmoc chemistry or by methyl, benzyl or phenyl in tBoc chemistry. Direct incorporation of phosphotyrosine without phosphate protection can also be used in Fmoc chemistry. In the post-assembly incorporation strategy, the unprotected hydroxyl group of Ser, Thr or Tyr is derivatized on solid phase with di-tert.butyl-, dibenzyl- or dimethyl-N,N'-diisopropylphosphoramidite and then oxidized by tert.butylhydroperoxide.

Solid phase synthesis is usually carried out from the carboxyl-terminus by coupling the alpha-amino protected (side-chain protected) amino acid to a suitable solid support. An ester linkage is formed when the attachment is made to a chloromethyl, chlortrityl or hydroxymethyl resin, and the resulting polypeptide will have a free carboxyl group at the C-terminus. Alternatively, when an amide resin such as benzhydrylamine or *p*-methylbenzhydrylamine resin (for tBoc chemistry) and Rink amide or PAL resin (for Fmoc chemistry) is used, an amide bond is formed and the resulting

- 16 -

polypeptide will have a carboxamide group at the C-terminus. These resins, whether polystyrene- or polyamide-based or polyethyleneglycol-grafted, with or without a handle or linker, with or without the first amino acid attached, are commercially available, and their preparations have been described by Stewart et al (1984)., "Solid Phase Peptide Synthesis" (2nd Edition), Pierce Chemical Co., Rockford, IL.; and Bayer & Rapp (1986) Chem. Pept. Prot. 3, 3; and Atherton, et al. (1989) Solid Phase Peptide Synthesis: A Practical Approach, IRL Press, Oxford.

10 The C-terminal amino acid, protected at the side-chain if necessary and at the alpha-amino group, is attached to a hydroxymethyl resin using various activating agents including dicyclohexylcarbodiimide (DCC), N,N'-diisopropylcarbodiimide DIPCDI) and carbonyldiimidazole (CDI). It can be attached to
15 chloromethyl or chlorotriyl resin directly in its cesium tetramethylammonium salt form or in the presence of triethylamine (TEA) or diisopropylethylamine (DIEA). First amino acid attachment to an amide resin is the same as amide bond formation during coupling reactions.

20 Following the attachment to the resin support, the alpha-amino protecting group is removed using various reagents depending on the protecting chemistry (e.g. , tBoc, Fmoc). The extent of Fmoc removal can be monitored at 300-320 nm or by a conductivity cell. After removal of the alpha-amino protecting
25 group, the remaining protected amino acids are coupled stepwise in the required order to obtain the desired sequence.

Various activating agents can be used for the coupling reactions including DCC, DIPCDI, 2-chloro-1,3-dimethylimidium hexafluorophosphate (CIP), benzotriazol-1-yl-oxy-tris-
30 (dimethylamino)-phosphonium hexafluorophosphate (BOP) and its pyrrolidine analog (PyBOP), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP), O -(benzotriazol-1-yl)-1,1,3,3-

- 17 -

tetramethyluronium hexafluorophosphate (HBTU) and its tetrafluoroborate analog (TBTU) or its pyrrolidine analog (HBTU), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) and its tetrafluoroborate analog (TATU) or pyrrolidine analog (HAPyU). The most common catalytic additives used in coupling reactions include 4-dimethylaminopyridine (DMAP), 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine (HODhbt), N-hydroxybenzotriazole (HOBt) and 1-hydroxy-7-azabenzotriazole (HOAt). Each protected amino acid is used in excess (>2.0 equivalents), and the couplings are usually carried out in N-methylpyrrolidone (NMP) or in DMF, CH₂Cl₂ or mixtures thereof. The extent of completion of the coupling reaction can be monitored at each stage, e.g., by the ninhydrin reaction as described by Kaiser et al., Anal. Biochem. 34:595 (1970). In cases where incomplete coupling is found, the coupling reaction is extended and repeated and may have chaotropic salts added. The coupling reactions can be performed automatically with commercially available instruments such as ABI model 430A, 431A and 433A peptide synthesizers.

After the entire assembly of the desired polypeptide, the polypeptide-resin is cleaved with a reagent with proper scavengers. The Fmoc peptides are usually cleaved and deprotected by TFA with scavengers (e.g., H₂O, ethanedithiol, phenol and thioanisole). The tBoc peptides are usually cleaved and deprotected with liquid HF for 1-2 hours at -5 to 0°C, which cleaves the polypeptide from the resin and removes most of the side-chain protecting groups. Scavengers such as anisole, dimethylsulfide and p-thiocresol are usually used with the liquid HF to prevent cations formed during the cleavage from alkylating and acylating the amino acid residues present in the polypeptide. The formyl group of Trp and dinitrophenyl group of His need to be removed, respectively, by piperidine and thiophenol in DMF prior to the HF cleavage. The acetamidomethyl group of Cys can

- 18 -

be removed by mercury(II) acetate and alternatively by iodine, thallium (III) trifluoroacetate or silver tetrafluoroborate which simultaneously oxidize cysteine to cystine. Other strong acids used for tBoc peptide cleavage and deprotection include

5 trifluoromethanesulfonic acid (TFMSA) and trimethylsilyltrifluoroacetate (TMSOTf).

Recombinant DNA methodology can also be used to prepare the polypeptides. The known genetic code, tailored if desired with known preferred codons for more efficient expression in a given host
10 organism, can be used to synthesize oligonucleotides encoding the desired amino acid sequences. The phosphoramidite solid support method of Matteucci *et al.*, *J. Am. Chem. Soc.* 103:3185 (1981) or other known methods can be used for such syntheses. The resulting oligonucleotides can be inserted into an appropriate vector and
15 expressed in a compatible host organism.

The polypeptides of the invention can be purified using HPLC, gel filtration, ion exchange and partition chromatography, countercurrent distribution or other well known methods. In a preferred embodiment of the present invention the covalent NS4A-NS3 complexes also contain
20 a histidine tag which facilitates purification using a Ni⁺ column as is illustrated below.

One can use the covalent NS4A-NS3 complexes of the invention, along with known synthetic substrates, to develop high throughput assays. These can be used to screen for compounds which inhibit
25 proteolytic activity of the protease. This is carried out by developing techniques for determining whether or not a compound will inhibit the covalent NS4A-NS3 complexes of the invention from cleaving the viral substrates. Examples of such synthetic substrates are set forth in SEQ ID NOs 25 and 93. If the substrates are not cleaved, the virus cannot
30 replicate. One example of such a high throughput assay is the scintillation proximity assay (SPA). SPA technology involves the use of beads coated with scintillant. Bound to the beads are acceptor molecules

- 19 -

such as antibodies, receptors or enzyme substrates which interact with ligands or enzymes in a reversible manner.

For a typical protease assay the substrate peptide is biotinylated at one end and the other end is radiolabelled with low energy emitters
5 such as ^{125}I or ^3H . The labeled substrate is then incubated with the enzyme. Avidin coated SPA beads are then added which bind to the biotin. When the substrate peptide is cleaved by the protease, the radioactive emitter is no longer in proximity to the scintillant bead and no light emission takes place. Inhibitors of the protease will leave the
10 substrate intact and can be identified by the resulting light emission which takes place in their presence.

Another type of protease assay, utilizes the phenomenon of surface plasmon resonance (SPR). A novel, high throughput enzymatic assay utilizing surface plasmon resonance technology has been
15 successfully developed. Using this assay, and a dedicated BIAcore™ instrument, at least 1000 samples per week can be screened for either their enzymatic activity or their inhibitory effects toward the enzymatic activity, in a 96 well plate format. This methodology is readily adaptable to any enzyme-substrate reaction. The advantage of this assay over the
20 SPA assay is that it does not require a radiolabeled peptide substrate.

EXAMPLES

Several covalent NS4A-NS3 complexes have been constructed, purified, characterized and assayed for activity based on a cDNA clone containing an HCV Japanese (1b/BK) strain whose sequence is published
25 in Takamizawa *et al.*, 1991, *J. Virology* 65:1105-1113. DNA sequencing of the clone (BK 138-1) revealed four amino acid differences with the published sequence, at positions 66 (A->G), 86 (P->Q), 87 (K->A) and 147 (F->S) of the NS3 protein.

The present invention can be illustrated by the following non-
30 limiting examples.

- 20 -

Reagents and General Methods

Plasmid pHCV-1b/BK can be derived from DNA fragments containing the entire DNA sequence of HCV BK cDNA as reported by Takamizawa *et al.*, 1991, *J. Virology* 65:1105-1113, with the above-mentioned changes. Plasmid pMD-34-2 is derived from that portion of the disclosed DNA sequence which encodes NS3 residues 1-631 from HCV BK cDNA.

Restriction Enzymes, Vent Polymerase and ThermoPol buffer were obtained from New England Biolabs (Beverly, MA). The QuickChange mutagenesis kit and dNTP's were obtained from Stratagene (LaJolla, CA). Ready-to-Go T4 DNA Ligase was obtained from Pharmacia Biotech (Piscataway, NJ). Oligonucleotide primers were synthesized by Genosys Biotechnologies (Woodland, Texas). DNA sequencing was performed according to the Sanger-Dideoxy method by Bioserve Biotechnologies (Laurel, MD). pET vectors and BL21(DE3) cells were obtained from Novagen (Madison, WI). PCR reactions were carried out in a Perkin Elmer Cetus, model 480 DNA thermocycler. DH5 α cells and TAE buffer were purchased from Gibco, BRL. GTG agarose was purchased from FMC corporation. The Qiaquick gel extraction kit and Qiaquick PCR purification kit were purchased from Qiagen Inc. (Chatsworth, CA).

Standard DNA recombinant DNA methods were carried out essentially as described by Sambrook *et. al.* in "Molecular Cloning: A Laboratory Manual," 2nd edition, 1989, Cold Springs Harbor Press, Plainview, New York.

- 21 -

Preparation of NS4A-Tethered Forms of HCV NS3 Protease*Native, NS4A-tethered forms of NS3 catalytic domain*

Various NS4A-tethered forms of the NS3 catalytic domain were constructed by joining the NS4A peptide GSVVIVGRIILS (NS4A amino acids 21-32) to the amino terminus of NS3 amino acids 3-181 via various three or four residue linkers, and were cloned into the pET-28b+ vector.

Single stranded oligonucleotide primers were designed to generate a 616 base pair PCR fragment containing an NdeI site followed by the NS4A peptide, a linker, and amino acids 3-181 of the NS3 catalytic domain at the 5' terminus and a stop codon flanked by an EcoRI site at the 3' terminus. The template used was the sequence disclosed in Takamizawa, *et al*, 1991, *J. Virology* 65(3):1105-1113, which contains the entire HCV genome from the 1b/BK strain, except for the four differences described above. Other sources for HCV DNA can be used in the disclosed methods, including plasmid pBRTM/HCV 1-3011 (Grakoui *et al.*, 1993), which contains the entire genome from the 1a strain.

Vent DNA polymerase was utilized to amplify the DNA by PCR. Primers were diluted in dH₂O to give a final concentration of 50 µg/ml. The template was diluted in dH₂O to give a final concentration of 10 ng/µl; The dNTP's (GTP, ATP, CTP, GGT) were diluted to a concentration of 10 mM (2.5 mM each) in dH₂O.

100 µl reactions were prepared for PCR in a 500 µl Eppendorf tube by addition of the following reagents: 74 µl of dH₂O, 10 µl of the 10x Thermopol buffer (final 1x buffer: 10 mM KCL, 20 mM Tris-HCL (pH 8.8), 2mM MgSO₄ and 0.1% Triton X), 10 µl of template (100 ng), 2 µl of the 5' primer (100 ng); 1 µl of the 3' primer (50 ng), 2 µl of the dNTP mixture (200 µM) and 1 µl of Vent polymerase enzyme (1 unit). The mixture was

- 22 -

then overlayed with 20 ul of immersion oil and placed in the thermocycler for amplification. The PCR conditions were as follows: 95 °C for 45 seconds (1 cycle); 95 °C for 30 seconds, 55 °C for 1 minute, 72 °C for 2 minutes (25 cycles).

5 The amplified 616 base pair fragment was purified in preparation for restriction digestion using a Qiaquick PCR purification kit according to the manufacturer's protocol without modification. Briefly, the aqueous layer was removed and placed in a 1.5 ml Eppendorf tube with a reagent that aids the DNA to bind to a column matrix. The DNA was
10 washed while bound to the column and then eluted with 43 µl of H₂O. The DNA was then double digested with EcoRI and NdeI in a 50 ul volume for 1 hour at 37 °C. The reaction took place in a 1.5 ml polypropylene Eppendorf tube with 5 µl of 10x EcoRI buffer (final concentration of 50mM NaCl, 100 mM Tris-HCL, 10mM MgCl₂, 0.25%
15 Triton X-100, pH 7.5) and 1 µl of EcoRI and NdeI (20 units). The pET-28b+ vector (3 µg) was also digested using the same conditions. The digests were further purified by resolving them on a 1.0 % agarose electrophoresis gel for 45 minutes under 100 volts. They were rendered visible with 0.5 µg/ml of ethidium bromide, excised with a scalpel under
20 short-wave UV, solubilized and purified using the QIAquick gel extraction kit according to manufacturer's protocol without modifications. The fragments were quantitated by visually comparing a 5 ul aliquot of the purified fragment versus Lambda Hind/III DNA standards on a 1% agarose gel. Approximately 200 ng of vector and 50 ng
25 of PCR fragment were ligated together in a 20 ul volume for 18 hours at 16 degrees. They were combined together in a T4 ligase (Ready-to-Go) reaction tube according to standard protocol without modifications.

2 µl of this mixture was then used to transform 50 µl of DH5α cells for plasmid propagation according to manufacturer's protocol.

- 23 -

Briefly, a 1.5 ml Eppendorf tube was placed on ice and 50 μ l of DH5 α cells (previously stored at -80°C and then thawed on ice immediately prior to use) were added to the tube along with the 2 μ l of ligation mixture and allowed to incubate for 30 minutes. They were then heat shocked for 1
5 minute at 42°C, returned to the ice for 2 minutes and then regenerated with 500 μ l of SOC medium and incubated at 37°C for 1 hour at 300 rpm.

200 μ l of these cells were then plated out on LB/20-10-5 agar (per liter: tryptone 50 grams, yeast extract 25 grams, NaCl 12.5 gram) with kanamycin (25 μ g/ml), spread for single colony isolation and incubated
10 at 37 °C overnight. Three single colonies were selected for plasmid preparations. They were inoculated into 100 mls of LB/20-10-5 broth with kanamycin (25 μ g/ml) in a 250 ml baffled flask and grown overnight for 18 hours at 37 degrees at 300 RPM in a shaker. The next
15 day, the cultures were spun down in 500 ml Nalgene centrifuge bottles (8000 RPM, 10 minutes, 4 °C) and the pellet was harvested for plasmid isolation. The Qiagen midi-prep kit was used according to manufacturer's protocol. The DNA was quantitated using a UV/VIS spectrophotometer (Perkin-Elmers) at 260 nm. The purified, plasmid-DNA isolates were sequenced on an Applied Biosystems 373A DNA
20 sequencer at Bioserve Biotechnologies, Inc. To confirm the sequence, both top and bottom strands were sequenced via primers that were synthesized by Bioserve Biotechnologies.

Native, NS4A-tethered forms of NS3 full-length domain

Both parental plasmids, HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁ and HIS-
25 NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁ /S139A parental plasmids were created via a cut and paste method. Briefly, 5 μ l of plasmid PMD34-2 (1 μ g), plasmid HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁ (5 μ g) and plasmid HIS-NS3₁₋₆₃₁/S139A (1 μ g) were each digested separately in a 1.5 ml Eppendorf tube with 5 μ l of NEB buffer #2 (at final concentration of 10mM Tris-HCL, 10mM MgCl₂,

SUBSTITUTE SHEET (rule 26)

- 24 -

50mM NaCl, 1mM DTT, pH 7.9), 0.5 µl of acetylated BSA (final concentration 100 µg/ml), 1 µl of XbaI (2 Units) and 38.5 µl of ddH₂O.

These digests were incubated at 37 °C for one hour at which time 2.5 µl of 2M NaCl (final concentration of 150mM) 45 µl of ddH₂O and 2.5 µl of BspMI (2 Units) were added to the digests and incubated for 2 more hours at 37 °C. The double digests were then resolved on 0.8 % agarose gels and the size and quantity of the fragments were determined. The agarose gels were electrophoresed in BioRad apparatus and the fragments were excised using a scalpel. The excised backbone fragments which were derived from PMD34-2 and HIS-NS3₁₋₆₃₁/S139A were each 7.1 KB and the insert from HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁ was 275 base pairs. Approximately 2 µl of 7.1 KB backbone (200 ng) and 1 µl of 225 bp insert (50 ng) were ligated together in a 20 µl volume for 18 hours at 16 °C. They were combined together in a T4 ligase (Ready-to-Go) reaction tube according to standard protocol without modifications. 2 µl of this mixture was then used to transform 50 µl of DH5α cells for plasmid propagation according to manufacturer's protocol.

Three single colonies of each construct were selected for miniprep plasmid isolations using a Qiagen miniprep kit. They were inoculated into 5 mls of LB/20-10-5 broth with ampicillin (100 µg/ml) in a 15 ml tubes and grown overnight for 18 hours at 37°C at 300 RPM in a shaker. The next day, the cultures were spun down 3000 RPM, 10 minutes, 4°C and the pellet was harvested for plasmid isolation. The clones were then assessed for recombination by digesting with BspMI and XbaI according to the conditions described above. The digests were resolved on a 1% agarose gel and only those constructs yielding a 225 bp and 7.1 KB bp fragment were chosen as positives. Cultures from the positive clones were inoculated into 100 mls of LB/20-10-5 broth with ampicillin (100 ug/ml) in a 250 ml baffled flask and grown overnight for 18 hours

SUBSTITUTE SHEET (rule 26)

- 25 -

at 37°C at 300 RPM in a shaker. The next day, the cultures were spun down in 500 ml Nalgene centrifuge bottles (8000 RPM, 10 minutes, 4°C) and the pellet was harvested for plasmid isolation. The Qiagen midi-prep kit was used according to manufacturer's protocol. The DNA was
5 quantitated using a UV/VIS spectrophotometer (Perkin-Elmers) at 260 nm. The purified plasmid-DNA isolates were sequenced at the restriction site junctions on an Applied Biosystems 373A DNA sequencer at Bioserve Biotechnologies, Inc.

Site-directed Mutants.

10 All site-directed mutations created in either NS4A-tethered forms of catalytic or full-length domain of NS3 protease were carried out using the quikchange site-directed mutagenesis kit (Stratagene) according to the manufacturer's protocol. For each mutation, two oligonucleotide
primers (10 picomoles each) containing the desired mutation were used
15 to amplify the entire plasmid encompassing the NS4A-tethered NS3 protease gene (50 or 100 ng/reaction) using pfu DNA polymerase (2.5 units/reaction) in a final reaction volume of 50 µl. The PCR conditions were as follows: 95 °C for 45 seconds (1 cycle); 95 °C for 30 seconds, 55 °C for 1 minute, 68 °C for 15 minutes (16 cycles). After amplification, the
20 reaction mixture was treated with 1 ul of DpnI (1 Unit) for 1 hour at 37 °C in order to digest the parental DNA.

One microliter of this digest was used to transform 50 µl of XLI Blue cells to repair nicks and propagate the mutated plasmid. Plasmid-DNA were purified and transformed into BL21 (DE3) cells for expression
25 studies.

- 26 -

EXAMPLE 1**NS3 Catalytic Domain Constructs****i. HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁ (SEQ ID NO: 1)**

HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁ was constructed by joining amino acids 21-32 of the NS4A peptide to the N-terminal domain of NS3 protease (NS3 amino acids 3-181) via the linker GSGS (SEQ ID NO: 21), and was cloned into the pET-28b+ vector as described above. The 5' primer reads as follows:

5'GATATACATATGGGTTCTGTTGTTATTGTTGGTAGAATTATTTTATCT
GGTAGTGGTAGTATCACGGCCTACTCCCAA 3' (SEQ ID NO:26).

The 3' primer reads as follows:

5' CTCAGCGAATTCTCAAGACCGCATAGTAGTTTCCAT 3' (SEQ ID NO:27).

ii. HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/I17K (SEQ ID NO: 2)

A single amino acid mutant of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁ was constructed by creating a point mutation at position 17 of the NS3 domain of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁ construct as described above. Two oligonucleotide primers, each complementary to opposite strands of the template were generated which contain the point mutation which alters amino acid number 17 (isoleucine) to a lysine. The top strand primer was as follows:

5'CGGGGCCTACTTGGTTGCAAGATCACTAGCCTTACAGGC 3'
(SEQ ID NO:28).

The bottom strand read as follows:

5' GCCTGTAAGGCTAGTGATCTTGCAACCAAGTAGGCCCCG 3'
(SEQ ID NO: 29).

The template, HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁, along with these two primers, were utilized in a PCR reaction to generate the point mutation.

5 (iii) HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/I18K (SEQ ID NO: 3)

A single amino acid mutant of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁ was constructed by creating a point mutation at position 18 of the NS3 domain of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁ construct as described above. Two oligonucleotide primers, each complementary to opposite strands of the template, were generated which contain the point mutation which alters amino acid number 18 (isoleucine) to a lysine. The top strand primer was as follows:

5' CGGGGCCTACTTGGTTGCATCAAGACTAGCCTTACAGGC 3'

(SEQ ID NO: 30).

15 The bottom strand reads as follows:

5' GCCTGTAAGGCTAGTCTTGATGCAACCAAGTAGGCCCCG 3'

(SEQ ID NO: 31).

The template, HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁, along with these two primers was utilized in a PCR reaction to generate the point mutation.

20 (iv) HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/I17K, I18K (SEQ ID NO: 4)

A single amino acid mutant of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/I18K was constructed by creating a point mutation at position 17 of the NS3 domain of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/I18K construct as described above. Two oligonucleotide primers, each complementary to opposite strands of the template, were generated which contain the point mutation which alters amino acid number 18 (isoleucine) to a lysine. The top strand primer was as follows:

- 28 -

5' CGGGGCCTACTTGGTTGCAAGAAGACTAGCCTTACAGGC 3'

(SEQ ID NO:32).

The bottom strand read as follows:

5' GCCTGTAAGGCTAGTCTTCTTGCAACCAAGTAGGCCCCG 3'.

5 (SEQ ID NO:33)

The template HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/I18K, along with these two primers, was utilized in a PCR reaction to generate the point mutation.

v. HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/S139A (SEQ ID NO: 5)

10 A single amino acid mutant of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁ was constructed by creating a point mutation at position 139 of the NS3 domain of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁ construct as described above. Two oligonucleotide primers, each complementary to opposite strands of the template, were generated which contain the point mutation
15 which alters amino acid number 139 (catalytic serine) to an alanine. The top strand primer was as follows:

5' CTCCTACTTGAAGGGCTCTGCTGGTGGTCCACTGCTCTGC 3'

(SEQ ID NO:34).

The bottom strand reads as follows:

20 5' GCAGAGCAGTGGACCACCAGCAGAGCCCTTCAAGTAGGAG 3'

(SEQ ID NO:35).

The template HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁, along with these two primers, was utilized in a PCR reaction to generate the point mutation.

25

SUBSTITUTE SHEET (rule 26)

- 29 -

vi. HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/S139A, I17K (SEQ ID NO: 6)

A single amino acid mutant of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/S139A was constructed by creating a point mutation at position 17 of the NS3 domain of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/S139A construct as described above. Two oligonucleotide primers, each complementary to opposite strands of the template, were generated which contain the point mutation which alters amino acid number 17 (isoleucine) to a lysine. The top strand primer was as follows:

5' CGGGGCCTACTTGGTTGCAAGATCACTAGCCTTACAGGC 3'
(SEQ ID NO:36).

The bottom strand reads as follows:

5' GCCTGTAAGGCTAGTGATCTTGCAACCAAGTAGGCCCCG 3'
(SEQ ID NO:37).

The template, HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/S139A, along with these two primers, was utilized in a PCR reaction to generate this point mutation.

vii. HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/S139A, I18K (SEQ ID NO: 7)

A single amino acid mutant of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/S139A was constructed by creating a point mutation at position 18 of the NS3 domain of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/S139A construct as described above. Two oligonucleotide primers, each complementary to opposite strands of the template, were generated which contain the point mutation which alters amino acid number 18 (isoleucine) to a lysine. The top strand primer was as follows:

5' CGGGGCCTACTTGGTTGCATCAAGACTAGCCTTACAGGC 3'
(SEQ ID NO:38).

- 30 -

The bottom strand reads as follows:

5' GCCTGTAAGGCTAGTCTTGATGCAACCAAGTAGGCCCCG 3'

(SEQ ID NO:39).

The template, HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/S139A along with these two
5 primers was utilized in a PCR reaction to generate this point mutation.

viii. HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/S139A, I17K, I18K (SEQ ID NO. 8)

A single amino acid mutant of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/S139A, I17K was constructed by creating a point mutation at position
18 of the NS3 domain of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/S139A, I17K
10 construct as described above. Two oligonucleotide primers, each
complementary to opposite strands of the template were generated
which contain the point mutation which alters amino acid number 18
(isoleucine) to a lysine. The top strand primer was as follows:

5' CGGGGCCTACTTGGTTGCAAGAAGACTAGCCTTACAGGC 3'

15 (SEQ ID NO: 40).

The bottom strand reads as follows:

5' GCCTGTAAGGCTAGTCTTGATGCAACCAAGTAGGCCCCG 3'

(SEQ ID NO: 41).

The template, HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/S139A, I17K, along with
20 these two primers, was utilized in a PCR reaction to generate this point
mutation.

ix. HIS-NS4A₂₁₋₃₂-PAGG-NS3₃₋₁₈₁ (SEQ ID NO: 9)

An NS4A-tethered form of the NS3 catalytic domain, HIS-NS4A₂₁₋₃₂-PAGG-NS3₃₋₁₈₁, was constructed by joining the NS4A peptide
25 GSVVIVGRIILS (NS4A amino acids 21-32) to the N-terminal domain of
NS3 protease (NS3 amino acids 3-181) via the linker PAGG (SEQ ID NO:

- 31 -

22), and was cloned into the pET-28b+ vector as described above. Primers were designed to generate a 616 base pair PCR fragment containing an NdeI site followed by the NS4A peptide, the PAGG linker, and amino acids 3-181 of the NS3 catalytic domain at the 5' terminus and a stop codon flanked by an EcoRI site at the 3' terminus. The 5' primer reads as follows:

5' GATATACATATGGGTTCTGTTGTTATTGTTGGTAGAATTATTTT

ATCTCCTGCTGGTGGTATCACGGCCTACTCCCAA 3' (SEQ ID NO: 42).

The 3' primer reads as follows:

10 5' CTCAGCGAATTCTCAAGACCGCATAGTAGTTTCCAT 3' (SEQ ID NO: 43).

Plasmid-DNA (PMD-34-2), comprised of pET-22b+ vector encompassing the gene insert encoding HIS-NS3 (1-631) from 1b/BK strain was used as the template for PCR.

15 x. **HIS-NS4A₂₁₋₃₂-PAGG-NS3₃₋₁₈₁/I17K (SEQ ID NO: 10)**

A single amino acid mutant of HIS-NS4A₂₁₋₃₂-PAGG-NS3₃₋₁₈₁ was constructed by creating a point mutation at position 17 of the NS3 domain of the HIS-NS4A₂₁₋₃₂-PAGG-NS3₃₋₁₈₁ construct as described above. Two oligonucleotide primers, each complementary to opposite strands of the template, were generated which contain the point mutation which alters amino acid number 17 (isoleucine) to a lysine. The top strand primer was as follows:

5' CGGGGCCTACTTGGTTGCAAGATCACTAGCCTTACAGGC 3'

(SEQ ID NO: 44).

25 The bottom strand reads as follows:

SUBSTITUTE SHEET (rule 26)

- 32 -

5' GCCTGTAAGGCTAGTGATCTTGCAACCAAGTAGGCCCCG 3'

(SEQ ID NO: 45).

The template, HIS-NS4A₂₁₋₃₂-PAGG-NS3₃₋₁₈₁, along with these two primers was utilized in a PCR reaction to generate this point mutation.

5 xi. **HIS-NS4A₂₁₋₃₂-PAG-NS3₃₋₁₈₁ (SEQ ID NO: 46)**

A NS4A-tethered form of the NS3 catalytic domain, HIS-NS4A₂₁₋₃₂-PAG-NS3₃₋₁₈₁, was constructed by joining the NS4A peptide GSVVIVGRIILS (NS4A amino acids 21-32) to the N-terminal domain of NS3 protease (NS3 amino acids 3-181) via the linker PAG (SEQ ID NO: 47), and was cloned into the pET-28b+ vector as described above. Primers were designed to generate a 613 base pair PCR fragment containing an NdeI site followed by the NS4A peptide, the PAG linker, and amino acids 3-181 of the NS3 catalytic domain at the 5' terminus and a stop codon flanked by an EcoRI site at the 3' terminus. The 5' primer reads as follows:

5' GATATACATATGGGTTCTGTTGTTATTGTTGGTAGAATTATTTT

ATCTCCTGCTGGTATCACGGCCTACTCCCAA 3' (SEQ ID NO: 48).

The 3' primer reads as follows:

5' CTCAGCGAATTCTCAAGACCGCATAGTAGTTTCCAT 3'

20 (SEQ ID NO: 49).

Plasmid-DNA (PMD-34-2), comprised of pET-22b+ vector encompassing the gene insert encoding HIS-NS3 (1-631) from 1b/BK strain was used as the template for PCR.

xii. **HIS-NS4A₂₁₋₃₂-PAG-NS3₃₋₁₈₁/I17K (SEQ ID NO: 50)**

25 A single amino acid mutant of HIS-NS4A₂₁₋₃₂-PAG-NS3₃₋₁₈₁ was constructed by creating a point mutation at position 17 of the NS3

- 33 -

domain of HIS-NS4A₂₁₋₃₂-PAG-NS3₃₋₁₈₁ construct as described above. Two oligonucleotide primers, each complementary to opposite strands of the template were generated which contains the point mutation which alters amino acid residue number 17 (isoleucine) to a lysine. The top strand primer was as follows:

5' CGGGGCCTACTTGGTTGCAAGATCACTAGCCTTACAGGC 3'

(SEQ ID NO: 51).

The bottom strand reads as follows:

5' GCCTGTAAGGCTAGTGATCTTGCAACCAAGTAGGCCCCG 3'

(SEQ ID NO: 52).

The template, HIS-NS4A₂₁₋₃₂-PAG-NS3₃₋₁₈₁ along with these two primers were utilized in a PCR reaction to generate this point mutation.

xiii. HIS-NS4A₂₁₋₃₂-GGS-NS3₃₋₁₈₁ (SEQ ID NO: 53)

An NS4A-tethered form of NS3 catalytic domain, HIS-NS4A₂₁₋₃₂-GGS-NS3₃₋₁₈₁ was constructed by joining the NS4A peptide GSVVIVGRIILS (NS4A amino acids 21-32) to the N-terminal domain of NS3 protease (NS3 amino acids 3-181) via the linker GGS (SEQ ID NO: 54), and was cloned into the pET-28b+ vector as described above. Primers were designed to generate a 613 base pair PCR fragment containing an NdeI site followed by the NS4A peptide, the GGS linker, and amino acids 3-181 of the NS3 catalytic domain at the 5' terminus and a stop codon flanked by an EcoRI site at the 3' terminus. The 5' primer reads as follows:

5' GATATACATATGGGTTCTGTTGTTATTGTTGGTAGAATTATTTT

ATCTGGTGGTTCTATCACGGCCTACTCCCAA 3' (SEQ ID NO: 55).

The 3' primer reads as follows:

5' CTCAGCGAATTCTCAAGACCGCATAGTAGTTTCCAT 3'

SUBSTITUTE SHEET (rule 26)

- 34 -

(SEQ ID NO: 56).

Plasmid-DNA (PMD-34-2), comprised of pET-22b+ vector encompassing the gene insert encoding HIS-NS3 (1-631) from 1b/BK strain was used as the template for PCR.

5 **xiv. HIS-NS4A₂₁₋₃₂-GGs-NS3₃₋₁₈₁/I17K (SEQ ID NO: 57)**

A single amino acid mutant of HIS-NS4A₂₁₋₃₂-GGs-NS3₃₋₁₈₁ was constructed by creating a point mutation at position 17 of the NS3 domain of HIS-NS4A₂₁₋₃₂-GGs-NS3₃₋₁₈₁ construct as described above. Two oligonucleotide primers, each complementary to opposite strands
10 of the template, were generated which contain the point mutation which alters amino acid number 17 (isoleucine) to a lysine. The top strand primer was as follows:

5' CGGGGCCTACTTGGTTGCAAGATCACTAGCCTTACAGGC 3'

(SEQ ID NO: 58).

15 The bottom strand reads as follows:

5' GCCTGTAAGGCTAGTGATCTTGCAACCAAGTAGGCCCCG 3'

(SEQ ID NO: 59).

The template, HIS-NS4A₂₁₋₃₂-GGs-NS3₃₋₁₈₁, along with these two primers, was utilized in a PCR reaction to generate this point mutation.

20

EXAMPLE 2

NS3 Full-Length Constructs

i. HIS-NS3₁₋₆₃₁/I17K (SEQ ID NO: 60)

A single amino acid mutant of HIS-NS3₁₋₆₃₁ was formed by
25 creating a point mutation at position 17 of NS3 protease using the Plasmid-DNA (PMD-34-2), comprised of pET-22b+ vector encompassing

- 35 -

the gene insert, encoding HIS- NS3₁₋₆₃₁ from 1b/BK strain as described above. Two oligonucleotide internal primers, each complementary to opposite strands of the template, were generated which contain the point mutation which alters amino acid number 17 (isoleucine) to a lysine.

5 The top strand primer was as follows:

5' CGGGGCCTACTTGGTTGCAAGATCACTAGCCTTACAGGC 3'

(SEQ ID NO: 61).

The bottom strand reads as follows:

5' GCCTGTAAGGCTAGTGATCTTGCAACCAAGTAGGCCCCG 3'

10 (SEQ ID NO: 62).

The template, plasmid-DNA (PMD-34-2), comprised of pET-22b+ vector encompassing the gene insert, encoding HIS-NS3₁₋₆₃₁ from 1b/BK strain, along with these two primers was utilized in a PCR reaction to generate this point mutation.

15 ii. HIS-NS3₁₋₆₃₁/I18K (SEQ ID NO: 63)

A single amino acid mutant of HIS-NS3₁₋₆₃₁ was formed by creating a point mutation at position 18 of NS3 protease using the Plasmid-DNA (PMD-34-2), comprised of pET-22b+ vector encompassing the gene insert, encoding HIS-NS3₁₋₆₃₁ from 1b/BK strain as described
20 above. Two oligonucleotide internal primers, each complementary to opposite strands of the template, were generated which contain the point mutation which alters amino acid number 18 (isoleucine) to a lysine. The top strand primer was as follows:

5' CGGGGCCTACTTGGTTGCATCAAGACTAGCCTTACAGGC 3'

25 (SEQ ID NO: 64).

The bottom strand reads as follows:

5' GCCTGTAAGGCTAGTGATCTTGCAACCAAGTAGGCCCCG 3'

SUBSTITUTE SHEET (rule 26)

(SEQ ID NO: 65).

The template, plasmid-DNA (PMD-34-2), comprised of pET-22b+ vector encompassing the gene insert, encoding HIS-NS3₁₋₆₃₁ from 1b/BK strain along with these two primers was utilized in a PCR reaction to generate
5 this point mutation.

iii. HIS-NS3₁₋₆₃₁/S139A (SEQ ID NO: 66)

A single amino acid mutant of HIS-NS3₁₋₆₃₁ was formed by creating a point mutation at position 139 of the NS3 protease using the Plasmid-DNA (PMD-34-2), comprised of pET-22b+ vector encompassing
10 the gene insert, encoding HIS-NS3₁₋₆₃₁ from 1b/BK strain as described above. Two oligonucleotide internal primers, each complementary to opposite strands of the template, were generated which contain the point mutation which altered amino acid number 139 (catalytic serine) to an alanine. The top strand primer was as follows:

15 5' CTCCTACTTGAAGGGCTCTGCTGGTGGTCCACTGCTCTGC 3'

(SEQ ID NO: 67).

The bottom strand reads as follows:

5' GCAGAGCAGTGGACCACCAGCAGAGCCCTTCAAGTAGGAG 3'

(SEQ ID NO: 68).

20 The template, plasmid-DNA (PMD-34-2), comprised of pET-22b+ vector encompassing the gene insert, encoding HIS-NS3₁₋₆₃₁ from 1b/BK strain along with these two primers was utilized in a PCR reaction to generate this point mutation.

iv. HIS-NS3₁₋₆₃₁/I403S (SEQ ID NO: 69)

25 A single amino acid mutant of HIS-NS3₁₋₆₃₁ was formed by creating a point mutation at position 403 of the NS3 protease using the Plasmid-DNA (PMD-34-2), comprised of pET-22b+ vector encompassing

- 37 -

the gene insert, encoding HIS-NS3₁₋₆₃₁ from 1b/BK strain as described above. Two oligonucleotide internal primers, each complementary to opposite strands of the template, were generated which contain the point mutation which alters amino acid number 403 (isoleucine) to a serine.

5 The top strand primer was as follows:

5' GTCCGTCATACCAACTTCCGGAGACGTCGTTGTCG 3'

(SEQ ID NO: 70).

The bottom strand reads as follows:

5' CGACAACGACGTCTCCGGAAGTTGGTATGACGGAC 3'

10 (SEQ ID NO: 71).

The template, plasmid-DNA (PMD-34-2), comprised of pET-22b+ vector encompassing the gene insert, encoding HIS-NS3₁₋₆₃₁ from 1b/BK strain along with these two primers was utilized in a PCR reaction to generate this point mutation.

15 v. HIS-NS3₁₋₆₃₁/NdeI (SEQ ID NO. 72)

A silent mutant of HIS-NS3₁₋₆₃₁ was formed to eliminate the internal NdeI restriction site within NS3 protease using the Plasmid-DNA (PMD-34-2), comprised of pET-22b+ vector encompassing the gene insert, encoding HIS-NS3₁₋₆₃₁ from 1b/BK strain as described above. Two
20 oligonucleotide internal primers, each complementary to opposite strands of the template, were generated which contain point mutations which alters the codons on the reading strand of alanine 217 from GCA to GCC and tyrosine 218 from TAT to TAC. The top strand primer was as follows:

25 5' ACTAAAGTGCCGGCTGCCTACGCAGCCCAAGGG 3'

(SEQ ID NO: 73).

The bottom strand reads as follows:

SUBSTITUTE SHEET (rule 26)

- 38 -

5' CCCTTGGGCTGCGTAGGCAGCCGGCACTTTAGT 3'

(SEQ ID NO: 74).

The template, plasmid-DNA (PMD-34-2), comprised of pET-22b+ vector encompassing the gene insert encoding HIS-NS3₁₋₆₃₁ from 1b/BK strain, along with these two primers, was utilized in a PCR reaction to generate this point mutation.

vi. HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁ (SEQ ID NO: 4)

An NS4A-tethered form of the NS3 full-length domain, HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁, was constructed via a cut and paste strategy as described above. Briefly, a 270 bp fragment was generated by restricting HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁ with XbaI/BspMI; This fragment encompassed sequences encoding a histidine tag followed by a thrombin site, the NS4A peptide, GSVVIVGRIILS (NS4A amino acids 21-32), the linker GSGS (SEQ ID NO: 21) and NS3 amino acids 3-48. A second 7111 bp fragment (7111 bp) was generated by restricting Plasmid-DNA (PMD-34-2), comprised of pET-22b+ vector encompassing the gene insert, encoding HIS-NS3 (1-631) from 1b/BK strain with XbaI/BspMI resulting in a fragment encompassing the pET 22b+ vector backbone in addition to amino acids 49- 631. These two fragments were then ligated together with T4 DNA ligase to form HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁.

vii. HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/I17K (SEQ ID NO: 12)

A single amino acid mutant of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁ was constructed by creating a point mutation at position 17 of the NS3 domain of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁ construct as described above. Two oligonucleotide primers, each complementary to opposite strands of the template, were generated which contain the point mutation which alters amino acid number 17 (isoleucine) to a lysine. The top strand primer was as follows:

SUBSTITUTE SHEET (rule 26)

- 39 -

5' CGGGGCCTACTTGGTTGCAAGATCACTAGCCTTACAGGC 3'

(SEQ ID NO: 75).

The bottom strand read as follows:

5' GCCTGTAAGGCTAGTGATCTTGCAACCAAGTAGGCCCCG 3'

5 (SEQ ID NO: 76).

The template, HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁ along with these two primers was utilized in a PCR reaction to generate this point mutation.

viii. HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/I18K (SEQ ID NO: 13)

10 A single amino acid mutant of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁ was constructed by creating a point mutation at position 18 of the NS3 domain of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁ construct as described above. Two oligonucleotide primers, each complementary to opposite strands of the template were generated which contained the point mutation which alters amino acid number 18 (isoleucine) to a lysine. The top
15 strand primer was as follows:

5' CGGGGCCTACTTGGTTGCATCAAGACTAGCCTTACAGGC 3'

(SEQ ID NO: 77).

The bottom strand reads as follows:

5' GCCTGTAAGGCTAGTGATGCAACCAAGTAGGCCCCG 3'

20 (SEQ ID NO: 78).

The template, HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁, along with these two primers was utilized in a PCR reaction to generate this point mutation.

ix. HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/I17K, I18K (SEQ ID: 14)

25 A double amino acid mutant of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁ was constructed by creating 2 point mutations at positions 17 and 18 of the

- 40 -

NS3 domain of the HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁ construct simultaneously as described above. Two oligonucleotide primers, each complementary to opposite strands of the template, were generated which contain the point mutations which alter amino acid numbers 17 (isoleucine) and 18 (isoleucine) to lysines. The top strand primer was as follows:

5' CGGGGCCTACTTGGTTGCAAGAAGACTAGCCTTACAGGC 3'

(SEQ ID NO: 79).

The bottom strand read as follows:

10 5' GCCTGTAAGGCTAGTCTTCTTGCAACCAAGTAGGCCCCG 3'

(SEQ ID NO: 80).

The template, HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁, along with these two primers, was utilized in a PCR reaction to generate this point mutation.

x. HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/S139A (SEQ ID NO: 15)

15 An NS4A-tethered form of NS3 full-length domain, HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/S139A, was constructed via a cut and paste strategy as described above. Briefly, a 290 bp fragment was generated by restricting HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁ with XbaI/BspMI; this fragment encompass sequence encoding a histidine tag, a thrombin site, amino acids 21-32 of the the NS4A peptide, the linker GSGS (SEQ ID NO. 21) and NS3 amino acids 3-48. A second 7111 fragment (7111 bp) was generated by restricting HIS-NS3₁₋₆₃₁/S139A construct with XbaI/BspmI resulting in a fragment encompassing the pET 22b+ vector backbone in addition to amino acids 49- 631. These two fragments were then ligated together with T4 DNA
20
25 ligase to form HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/S139A.

- 41 -

xi. HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/S139A, I17K (SEQ ID NO: 16)

A single amino acid mutant of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/S139A was constructed by creating a point mutation at position 17 of the NS3 domain of the HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/S139A construct as described above. Two oligonucleotide primers, each complementary to opposite strands of the template, were generated which contain the point mutation which alters amino acid number 17 (isoleucine) to a lysine. The top strand primer was as follows:

5' CGGGGCCTACTTGGTTGCAAGATCACTAGCCTTACAGGC 3'

10 (SEQ ID NO: 81).

The bottom strand is as follows:

5' GCCTGTAAGGCTAGTGATCTTGCAACCAAGTAGGCCCCG 3'

(SEQ ID NO: 82).

The template HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/S139A, along with these two primers, was utilized in a PCR reaction to generate this point mutation.

xii. HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/S139A, I18K (SEQ ID NO: 17)

A single amino acid mutant of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/S139A was constructed by creating a point mutation at position 18 of the NS3 domain of the HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/S139A construct as described above. Two oligonucleotide primers, each complementary to opposite strands of the template, were generated which contain the point mutation which alters amino acid number 18 (isoleucine) to a lysine. The top strand primer was as follows:

5' CGGGGCCTACTTGGTTGCATCAAGACTAGCCTTACAGGC 3'

25 (SEQ ID NO: 83).

The bottom strand read as follows:

SUBSTITUTE SHEET (rule 26)

- 42 -

5' GCCTGTAAGGCTAGTCTTGATGCAACCAAGTAGGCCCCG 3'

(SEQ ID NO: 84).

The template HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/S139A, along with these two primers, was utilized in a PCR reaction to generate this point mutation.

5 **xiii. HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/S139A, I17K, I18K (SEQ ID NO: 18)**

10 A single amino acid mutant of HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/S139A, I17K was constructed by creating a point mutation at position 18 of the NS3 domain of the HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/S139A, I17K construct as described above. Two oligonucleotide primers, each complementary to opposite strands of the template, were generated which contain the point mutation which alters amino acid number 18 (isoleucine) to an lysine. The top strand primer was as follows:

5' CGGGGCCTACTTGGTTGCAAGAAGACTAGCCTTACAGGC 3'

(SEQ ID NO: 85).

15 The bottom strand reads as follows:

5' GCCTGTAAGGCTAGTCTTCTTGCAACCAAGTAGGCCCCG 3'

(SEQ ID NO: 86).

20 The template HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/S139A,I17K, along with these two primers was utilized in a PCR reaction to generate this point mutation.

xiv. HIS-NS4A₁₅₋₃₂-GSGS-NS3₃₋₆₃₁ (SEQ ID NO: 19)

25 A NS4A-tethered form of NS3 full-length domain, HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁ was constructed by joining the amino acids 15-32 of NS4A peptide to the N-terminal end of the NS3 protease (NS3 amino acids 3-631) via the linker GSGS, and was cloned into the pET-28b+ vector as described above with the following modification. Primers were designed to generate a PCR fragment containing an NdeI site followed by the

SUBSTITUTE SHEET (rule 26)

- 43 -

NS4A peptide, the GSGS linker (SEQ ID NO: 21), and amino acids 3-631 of the NS3 catalytic domain at the 5' terminus and a stop codon flanked by an EcoRI site at the 3' terminus. The 5' primer sequence was as follows:

5 5'GATATACATATGGCTTACTCTCTGACTACGGGTTCTGTTGTTATT
 GTTGGTAGAATTATTTTATCTGGTAGTGGTAGTATCACGGCCTACTCCCAA 3'
 (SEQ ID NO: 87).

The 3' primer sequence was as follows:

10 5' GTGGTGGTGCTCGAGGCTGCCGCGCGGCA
 CCAGCGTAACGACCTCCAGGTC 3' (SEQ ID NO: 88).

The template used was HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁. The resulting PCR fragment was 1974 bases. Vent DNA polymerase was employed and a final concentration of 200 µM dNTPS was used. The PCR
 15 conditions were as follows: 95 °C for 45 seconds (1 cycle); 95 °C for 30 seconds, 55 °C for 1 minute, 72 °C for 2 minutes (25 cycles). The product was purified with QIAquick PCR kit (Qiagen). This PCR product, along with the 6.6 kb vector backbone (HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁), were double digested with NdeI and BamHI. The digested fragments of 1.43
 20 and 6.6 Kbp respectively were run on agarose gel, excised, and column purified with QIAquick gel extraction kit (Qiagen). They were quantitated and then ligated together with T4 DNA ligase.

xv. HIS-NS4A₁₅₋₃₂-GSGS-NS3₃₋₆₃₁/S139A (SEQ ID NO: 20)

25 An NS4A-tethered form of NS3 full-length domain, HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/S139A was constructed by joining amino acids 15-32 of the NS4A peptide to the N-terminal end of the NS3 protease (NS3 amino acids 3-631) via the linker GSGS (SEQ ID NO: 21), and was cloned

- 44 -

into the pET-28b+ vector as described above with the following modification. Primers were designed to generate a PCR fragment containing an NdeI site followed by the NS4A peptide, the GSGS linker (SEQ ID NO: 21), and amino acids 3-631 of the NS3 catalytic domain at the 5' terminus and a stop codon flanked by an EcoRI site at the 3' terminus. The 5' primer sequence was as follows:

5'GATATACATATGGCTTACTCTCTGACTACGGGTTCTGTTGTTATT

GTTGGTAGAATTATTTTATCTGGTAGTGGTAGTATCACGGCCTACTCCCAA 3'

(SEQ ID NO: 89).

10 The 3' primer reads as follows:

5' TGGTGGTGCTCGAGGCTGCCGCGCGGCACCAGCGTAACGACCT

CCAGGTC 3' (SEQ ID NO: 90).

The template used was HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/S139A. The resulting PCR fragment was 1974 bases. Vent DNA polymerase was employed and a final concentration of 200 µM dNTPS was used. The PCR conditions were as follows: 95 °C for 45 seconds (1 cycle); 95 °C for 30 seconds, 55 °C for 1 minute, 72 °C for 2 minutes (25 cycles). The product was purified with QIAquick PCR kit (Qiagen). This PCR product along with the 6.6 kb vector backbone (HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁) were double digested with NdeI and BamHI. The digested fragments of 1.43 and 6.6 Kbp respectively were run on agarose gel, excised, and column purified with QIAquick gel extraction kit (Qiagen). They were quantitated and then ligated together with T4 DNA ligase.

EXAMPLE 3

Expression and Purification of HCV NS4A-NS3 Complexes

A. Small Scale Expression Studies

All constructed plasmids were transformed into DH5 α cells for
5 production of large amount of plasmid-DNA. The purified plasmid-DNA was transformed into BL21(DE3) cells for expression studies. The cells were grown in Terrific Broth in baffled flasks at 37°C to an OD of 1.0 and the temperature was lowered to 23°C. The cultures were induced with 0.4 mM IPTG and were harvested 3 hours after induction. Cells
10 were sonicated for 1 min in 50 mM HEPES, pH 7.5, 20% glycerol, 0.1% β OG, 0.3 M NaCl, 10 mM β ME and spun at 13,000 rpm for 10 min. The supernatants were analyzed on 10% Novex SDS-PAGE.

B. Large-Scale Expression And Purification Of NS4A-Tethered Forms Of HCV NS₃₋₁₈₁ Protease

15 *E. coli*, BL21(DE3) cells harboring either plasmid pET-22b or pET-28b encoding various native, single, or multiple mutants of NS4A-tethered forms of NS₃₋₁₈₁ were grown at 37°C in Terrific Broth supplemented with either 100 ug/ml of ampicillin (for pET-22b) or 25 ug/ml kanamycin (for pET28-b) in 10-liter fermentor. When the cell
20 density reaches an OD of 2-3, the temperature was lowered to 23°C within 5 minutes and cells were induced with 0.4 mM IPTG. Cells were harvested 3 hours after induction and frozen at -20 °C prior to purification.

Cell pellets were resuspended in 600 ml of lysis buffer containing
25 50 mM HEPES, pH 7.4, 10% glycerol, 0.3 M NaCl, 0.1% β OG, 2 mM β ME (buffer A), homogenized using a cell homogenizer (Omni Mixer ES) for 2 min and the cells were disrupted by two passes through a Microfluidizer (Microfluidics Model #M-110F) at 10,000 p.s.i. The lysate was centrifuged at 85,000 x g for 45 min. The supernatant was filtered

- 46 -

through 0.8 micron filter units (Nalgene) and applied at 40 ml/min to a 11-ml Ni-imidodiacetate (POROS 20 MC resin) column in the presence of 20 mM imidazole on BIOCAD (Perseptive Biosystems). The column was washed with 10 column volumes of buffer A, followed by
5 15 column volume of buffer A containing 1.0 M NaCl and 20 mM imidazole (buffer B). The bound protease was eluted with the elution buffer (buffer B containing 250 mM imidazole). The eluted fractions containing the protease were pooled and dialyzed versus 16 liters of 50 mM HEPES, pH 7.4, 10% glycerol, 1 M NaCl, 10 mM β ME in order to
10 remove the imidazole and the detergent.

When the removal of the N-terminal histidine tag was required, human thrombin (Enzyme Research) was added to the eluted, pooled fractions at a thrombin:protease ratio of 8 units per mg of protease and thrombin cleavage was allowed to proceed during the dialysis step for 18
15 hours. The dialyzed, thrombin-cleaved protease was applied to 3 sephacryl-100 sizing column (26 x 60cm, Pharmacia) in series, equilibrated in of 50 mM HEPES, pH 7.4, 10% glycerol, 1 M NaCl, 10 mM β ME at 0.5 ml/min. Fractions containing purified protease at above >95% homogeneity as judged by SDS-PAGE were pooled and flash-
20 frozen at -80 °C

C. *Large-Scale Expression And Purification Of NS4A-Tethered Forms Of HCV NS3₃₋₆₃₁ Protease*

E. coli, BL21(DE3) cells harboring either plasmid pET-22b or pET-28b encoding various native, single, or multiple mutants of NS4A-tethered forms of NS3₁₋₁₈₁ were grown at 37°C in Terrific Broth
25 supplemented with either 100 μ g/ml of ampicillin (for pET-22b) or 25 μ g/ml kanamycin (for pET28-b) in 10-liter fermentor. When the cell density reaches an OD of 2-3, the temperature was lowered to 23°C within 5 minutes and cells were induced with 0.4 mM IPTG. Cells were

- 47 -

harvested 3 hours after induction and frozen at -20 °C prior to purification.

Cell pellets were resuspended in 600 ml of lysis buffer containing 50 mM HEPES, pH 7.4, 10% glycerol, 0.3 M NaCl, 0.1% β OG, 2 mM β ME (buffer A), homogenized using a cell homogenizer (Omni Mixer ES) for 2 min and the cells were disrupted by two passes through a Microfluidizer (Microfluidics Model #M-110F) at 10,000 p.s.i. The lysate was centrifuged at 85,000 x g for 45 min. The supernatant was filtered through 0.8 micron filter units (Nalgene) and applied at 40 ml/min to a 11-ml Ni-imidodiacetate (POROS 20 MC resin) column in the presence of 20 mM imidazole on BIOCAD (Perseptive Biosystems). The column was washed with 10 column volumes of buffer A, followed by 15 column volume of buffer A containing 1.0 M NaCl and 20 mM imidazole (buffer B). The bound protease was eluted with the elution buffer (buffer B containing 250 mM imidazole). The eluted fractions containing the protease were pooled and dialyzed versus 16 liters of 50 mM HEPES, pH 7.4, 10% glycerol, 1 M NaCl, 10 mM β ME in order to remove the imidazole and the detergent.

When the removal of the N-terminal histidine tag was required, human thrombin (Enzyme Research) was added to the eluted, pooled fractions at a thrombin:protease ratio of 8 units per mg of protease and thrombin cleavage was allowed to proceed during the dialysis step for 18 hours. The dialyzed, thrombin-cleaved protease was applied to 3 sephacryl-100 sizing column (26 x 60cm, Pharmacia) in series, equilibrated in of 50 mM HEPES, pH 7.4, 10% glycerol, 1 M NaCl, 10 mM β ME at 0.5 ml/min. Fractions containing purified protease at above >95% homogeneity as judged by SDS-PAGE were pooled and flash-frozen at -80 °C.

EXAMPLE 4**Molecular Weight Determination Of Various NS3 Protease Forms
By Size Exclusion Chromatography**

Two hundred µl of various purified proteins were applied to a
 5 calibrated Superdex-75 HR (1cm x 30 cm) FPLC column equilibrated with
 25 mM HEPES, pH 7.4, 1M NaCl and 10% glycerol and 10 mM βME at 0.5
 ml/min. The column was precalibrated using Pharmacia standard
 calibration proteins (BSA: 67 KDa; Ovalbumin: 43 KDa;
 Chymotrypsinogen A: 31 KDa; Ribonuclease A: 13.7 KDa). Protein
 10 elution was monitored at 280 nm.

The following covalent NS4A-NS3 complexes described above
 were characterized by the above method:

HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁
 HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/I17K
 15 HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/I18K
 HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/S139A
 HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/S139A, I17K
 HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₁₈₁/S139A, I18K

 HIS-NS4A₂₁₋₃₂-PAGG-NS3₃₋₁₈₁
 20 HIS-NS4A₂₁₋₃₂-PAGG-NS3₃₋₁₈₁/I17K

 HIS-NS4A₂₁₋₃₂-PAG-NS3₃₋₁₈₁/I17K

 HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁.
 HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/I17K
 HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/I18K
 25 HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/S139A
 HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/S139A, I17K
 HIS-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁/S139A, I18K

Of those constructs characterized, all covalent NS4A-NS3
 complexes containing a three amino acid linker resulted in aggregated
 30 forms, as judged by size exclusion chromatography. NS4A-tethered
 forms in which a point mutation at position 17 or 18 had not been
 introduced also resulted in aggregated forms, although they exhibited
 activity identical to that of the monodispersed forms of the protease.

- 49 -

Covalent NS4A-NS3 complexes which contained a four amino acid linker and a point mutation at position 17 and/or 18 resulted in active, monodispersed proteins with apparent molecular weights smaller than predicted as determined by size exclusion chromatography.

5

EXAMPLE 5
Determination of Proteolytic Activity

Following expression and purification, newly engineered recombinant species were assayed for proteolytic activity utilizing a 1D-HPLC (reverse-phase chromatography) technique. Assays were
10 conducted using the 5A/5B (P8P8') substrate DTEDVVCC*SMSYTWGK (SEQ ID NO: 25) in 25 mM Tris-HCl pH 7.5, 150 mM NaCl, 0.5 mM EDTA, 10 mM DTT, 10% glycerol, and 0.05% lauryl maltoside. Concentration of all proteins were determined by BIORAD dye method). The catalytic domain His-NS3₁₋₁₈₁ (batch # 51072-92E) was preincubated at
15 a concentration of 250 nM in the presence of 20 μ M 4A peptide (KKGSVVIVGRIVLSGKPAIIPKK) for 15 minutes at 4°C. This mixture was then diluted into the reaction volume at a final concentration of 8 μ M 4A peptide and 100 nM catalytic domain. Reactions were incubated at room temperature for 60 minutes and were quenched with an equal
20 volume of 10% phosphoric acid. Following injection, cleavage products were monitored under a linear 0-80% acetonitrile gradient in 0.1% TFA. The product P1'P8'K peak areas were automatically converted to product quantity in nanomoles by a standard curve.

25 The various covalent NS4A-NS3 complexes whose proteolytic efficiency has been determined according to the above method, and the results of each determination, are shown in Table 1.

Table 1.
Catalytic Efficiency Of Various Forms Of NS3 Protease

Construct	k_{cat} (min^{-1})	K_{m} (μM)	$k_{\text{cat}}/K_{\text{m}}$ ($\text{M}^{-1} \text{s}^{-1}$)
NS3 ₁₋₆₃₁ -NS4A ₁₋₅₄	10 ± 2	20 ± 2	$(8 \pm 2) \times 10^3$
His-NS3 ₁₋₁₈₁ + NS4A Peptide ^a	3 ± 1	80 ± 20	$(0.5 \pm 0.2) \times 10^3$
His-NS4A ₂₁₋₃₂ -GSGS-NS3 ₃₋₁₈₁	9 ± 2	19 ± 3	$(8 \pm 2) \times 10^3$
His-NS4A ₂₁₋₃₂ -GSGS-NS3 ₃₋₁₈₁ /I17K	16 ± 3	20 ± 2	$(14 \pm 2) \times 10^3$
His-NS4A ₂₁₋₃₂ -GSGS-NS3 ₃₋₁₈₁ /I18K	10 ± 2	22 ± 2	$(8 \pm 2) \times 10^3$

5

^a [E] = 0.25 μM , [NS4A Peptide] = 10 μM

As can be seen from the forgoing results, all covalent NS4A-NS3 complexes were shown to have an equivalent catalytic efficiency to that of full-length NS3₁₋₆₃₁-NS4A₁₋₅₄. In contrast, the non-covalent complex of NS3₁₋₁₈₁ with the NS4A peptide (0.1:8 μM), KK-(NS4A₂₁₋₃₉)-KK, had an catalytic activity which is 8 fold lower than the full-length NS3₁₋₆₃₁-NS4A₁₋₅₄.

15

Example 6
High Throughput Screening Assays
Using Covalent NS4A-NS3 Complexes

The claimed covalent NS4A-NS3 complexes are useful in screening methods for identifying NS3 protease inhibitors. One such method in which the claimed covalent complexes can be used is illustrated below.

25

Surface Plasmon Resonance Assay

The present example illustrates a method for determining if a compound can be useful as an HCV protease inhibitor using the surface plasmon resonance assay. Figures 5A and 5B schematically depict the technique.

- 51 -

BIAcore™ is a processing unit for Biospecific Interaction Analysis. The processing unit integrates an optical detection system with an autosampler and a microfluidic system. BIAcore™ uses the optical phenomena of surface plasmon resonance to monitor interaction
5 between biomolecules.

SPR is a resonance phenomenon between incoming photons and electrons on the surface of thin metal film. Resonance occurs at a sharply defined angle of incident light. At this angle, called the resonance angle, energy is transferred to the electrons in the metal film, resulting in a
10 decreased intensity of the reflected light. SPR response depends on a change in refractive index in the close vicinity of the sensor chip surface, and is proportional to the mass of analyte bound to the surface. The BIAcore™ continuously measures the resonance angle by a relative scale of resonance units (RU) and displays it as an SPR signal in a sensorgram,
15 where RU are plotted as a function of time.

BIAcore™ uses continuous flow technology. One interactant is immobilized irreversibly on the sensor chip, comprising a non-crosslinked carboxymethylated dextran providing a hydrophilic environment for bimolecular interaction. Solution containing the other
20 interactant flows continuously over the sensor chip surface. As molecules from the solution bind to the immobilized ligand, the resonance angle changes resulting in a signal registered by the instrument.

In this methodology, the enzymatic reactions are carried out
25 outside of the BIAcore™, in reaction tubes or 96-well tissue culture plates, as it is conventionally done for any of the other available high throughput assays. The SPR is only used as a detection means for determination of the amount of an intact substrate remaining in a solution after the reaction is quenched.

30 In order to measure the amount of the intact substrate prior to the addition of enzyme, a means of capturing the substrate onto the sensor chip had to be established. In addition, to satisfy the requirement for a

- 52 -

high throughput assay on the BIAcore™, the substrate needed to be removed from the surface after completion of analysis, so that the same surface can be used for subsequent reactions. To accomplish these two requirements, a phosphotyrosine is synthetically attached to one end of the substrate. The phosphotyrosine was chosen due to the commercial availability of an anti-phosphotyrosine monoclonal antibody. The antibody is covalently attached to the sensor chip by standard amine coupling chemistry. The anti-phosphotyrosine antibody, bound permanently to the chip, is used to capture the phosphotyrosine in a reversible manner. The antibody-phosphotyrosine interaction is ultimately used to capture and release the attached peptide substrate. After completion of analysis, the surface can be regenerated using various reagents such as 2 M MgCl₂.

When an intact peptide substrate is introduced onto the antibody surface, a large mass is detected by the instrument. To follow the extent of peptide cleavage, a mixture of peptide substrate and enzyme is incubated for the desired time and then quenched. Introduction of this mixture, containing both cleaved peptide and intact peptide, to a regenerated antibody surface results in detection by the instrument of a lower mass than that detected for the sample containing only intact peptide. The difference in the two values is then used to calculate the exact amount of intact peptide remaining after cleavage by the enzyme.

Although the reduction in mass can be directly followed with many large substrates, due to the small mass of a typical synthetic peptide substrate (10-20 amino acids, 1-3 Daltons), the mass difference, and thus the signal difference between the intact and cleaved peptide, is very small within the signal to noise ratio of the instrument. To circumvent this low sensitivity, a biotin can be attached at the N-terminus of the peptide. Streptavidin can then be added, thus tagging the peptide. When the tagged peptide is introduced onto the antibody surface of the chip, the signal will be higher. The signal resulting from

- 53 -

introduction of a cleaved peptide which lacks the N-terminal half, (and thus the streptavidin), will be much lower.

To carry out this method, an HCV protease 5A-5B peptide substrate, (such as 5A/5B substrate DTEDVVACSMSYTWYG-K (SEQ ID NO: 91)) is synthesized with an additional phosphotyrosine at the C-terminus and a biotin at the N-terminus. The biotin is then tagged with streptavidin. An anti-phosphotyrosine monoclonal antibody, 4G10 (Upstate Biotechnology Inc., Lake Placid, New York) is coupled to the sensor chip. In the absence of an active, uninhibited HCV protease, introduction of the intact phosphotyrosine peptide results in a large signal (large mass unit/large signal) through its interaction with the anti-phosphotyrosine monoclonal antibody (Mab).

The protease-catalyzed hydrolysis of the phosphotyrosine-biotinylated peptide is carried out in a 96 well plate. The reaction is stopped with an equal volume of mercuribenzoate. The cleaved peptide which lacks the tagged streptavidin (less mass) results in the loss of response units (lower signal).

Using this method, numerous compounds can be tested for their inhibitory activity since the antibody surface can be regenerated repetitively with 2 M MgCl_2 .

Procedure for Coupling Anti-phosphotyrosine Mab to the Sensor Chip

The anti-phosphotyrosine Mab is coupled to the carboxymethylated dextran surface of a sensor chip in the following manner. The flow rate used throughout the coupling procedure is 5 $\mu\text{l}/\text{min}$. The surface is first activated with a 35 μl injection of NHS/EDC (N-hydroxysuccinimide/N-dimethylaminopropyl-N'-ethylcarbodiimide-HCl). This is followed by a 40 ml injection of Mab 4G10 at 50 $\mu\text{g}/\text{ml}$ in 10 mM sodium acetate buffer, pH=4.0. Any remaining activated esters are then blocked by the injection of 35 μl of 1 M ethanolamine. These conditions result in the immobilization of approximately 7,500 response units (420 μM) of antibody.

Binding of Peptide and Regeneration of Mab 4G10 Surface

The flow rate used throughout the BIAcore analysis run is 5
5 $\mu\text{l}/\text{min}$. A 4 μl injection containing streptavidin-tagged peptide (peptide
concentration at 2 μM , streptavidin binding sites concentration at 9 μM) is
carried out. The amount of streptavidin-tagged peptide bound to the
antibody surface (in response units) is measured 30 seconds after the
injection is complete.

10

Regeneration of sensor chip surface

Regeneration of the Mab 4G10 surface is achieved using a 4 μl
pulse of 2 M MgCl_2 after each peptide injection. Surfaces regenerated up
15 to 500 times still showed 100% binding of tagged peptide.

Determination of the Optimal Concentration of Peptide and Streptavidin

20 To determine the optimal peptide concentration, a standard curve
was generated using various amounts of peptide (0-10 μM) in the
presence of excess streptavidin. A value in the linear range, 2 μM , was
chosen for standard assay conditions.

The amount of streptavidin required to completely tag the peptide
25 is determined using a peptide concentration of 2.5 μM and titrating the
amount of streptavidin (μM of binding sites). All the peptides were
shown to be completely tagged when streptavidin concentrations greater
than 3 μM (approximately equimolar to the peptide concentration) were
used. A streptavidin concentration of 9 μM (a 4.5 fold excess) was
30 chosen for standard assay conditions.

Application of Described Methodology to Covalent HCV NS4A-NS3 Complexes

35

The HCV protease 5A/5B peptide substrate, (such as 5A/5B
substrate DTEDVVACSMSYTWYG-K (SEQ ID NO: 91)), with a

- 55 -

phosphotyrosine synthetically attached to the C-terminus and a biotin attached at the N-terminus, is synthesized. Anti-phosphotyrosine monoclonal antibody, 4G10 is coupled to the sensor chip.

In the absence of active, uninhibited covalent HCV NS4A-NS3 complex, the introduction of the intact streptavidin-tagged biotinylated phosphotyrosine peptide to the sensor chip results in a large signal (large mass unit/large response units) through its interaction with the anti-phosphotyrosine monoclonal antibody.

The protease-catalyzed hydrolysis of the phosphotyrosine-biotinylated peptide is carried out with and without a suspected inhibitor in a 96 well plate. The reaction is stopped with an equal volume of the quenching buffer containing mercuribenzoate. Streptavidin is then added to tag the peptide. The cleaved peptide, which lacks the streptavidin (less mass), results in the loss of response units.

Using this assay, numerous compounds can be tested for their inhibitory activity since the antibody surface can be regenerated repetitively with 2 M $MgCl_2$.

Standard Operating Procedure for BIAcore-based HCV Assay

Reactions are prepared in a 96-well tissue culture plate using the Reaction Buffer (50 mM HEPES, pH 7.4, 20 % glycerol, 150 mM NaCl, 1mM EDTA, 0.1% Tween-20, 1 mM DTT) as diluent. The final reaction volume is 100 μ l. Sample with the peptide alone (Biotin-DTEDVVAC SMSYTWTKpY) is prepared by addition of 10 μ l of peptide stock at 100 μ M (prepared in the reaction buffer) to 90 μ l of reaction buffer, so that the final concentration of peptide is 10 μ M. Samples comprised of peptide and the covalent NS4A-NS3 complexes are prepared by addition of 10 μ l of peptide stock at 100 μ M and 10 μ l of covalent NS4A-NS3 stock at 0.17 mg/ml (both prepared in the reaction buffer) to 80 μ l of reaction buffer, so that the final concentration of peptide and the enzyme is 10 and 0.1 μ M respectively. The reaction is held at 30°C for the specified time and then quenched. Quenching is achieved by transferring a 20- μ l

Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala
 355 360 365
 Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu Ile Phe Cys His
 370 375 380
 Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu Ser Gly Leu Gly
 385 390 395 400
 Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro
 405 410 415
 Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala Leu Met Thr Gly
 420 425 430
 Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr
 435 440 445
 Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr
 450 455 460
 Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg Arg Gly Arg Thr
 465 470 475 480
 Gly Arg Gly Arg Arg Gly Ile Tyr Arg Phe Val Thr Pro Gly Glu Arg
 485 490 495
 Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala
 500 505 510
 Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr Ser Val Arg Leu
 515 520 525
 Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu
 530 535 540
 Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His Ile Asp Ala His
 545 550 555 560
 Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe Pro Tyr Leu Val
 565 570 575
 Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser
 580 585 590
 Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His
 595 600 605
 Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Val
 610 615 620
 Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala Cys Met Ser Ala
 625 630 635 640
 Asp Leu Glu Val Val Thr *

SUBSTITUTE SHEET (rule 26)

- 57 -

activity using a scintillation proximity assay (SPA, Amersham Life Science Inc., Arlington Height, IL). The unwinding activity present in this covalent His-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁ complex was compared with that of the full length His-NS3₁₋₆₃₁-NS4A₁₋₅₄ complex under their

5 corresponding optimal buffer conditions. The double stranded RNA substrate (Oligos, Etc., Inc. Wilsonville, OR) used in the assay contained a template 5'-GCU CGC CCG GGG AUC CUC UAG GAA UAC ACG UUC GAU-3' (SEQ ID NO: 121) annealed to a primer 5'-CUA GAG GAU CCC CGG GCG AGC CCU AUA GUG AGU CGU-3' (complementary

10 sequences of the template and the primer are underlined). This substrate is end-labeled with ³³P using T4 polynucleotide kinase.

The assay conditions for the covalent His-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁ complex were 100 mM MOPS [pH 7.0], 0.5 mM MgCl₂, 2 mM ATP, 0.5 mM DTT, 100 mg/ml BSA, 2% dimethylsulfoxide (DMSO) and 1 U

15 RNase inhibitor (5 prime->3 prime, Inc., Boulder, CO). For the full length His-NS3₁₋₆₃₁/NS4A₁₋₅₄ complex, the assay conditions were 100 mM PIPES [pH 6.0], 1 mM MgCl₂, 2 mM ATP, 0.6 mM DTT, 100 mg/ml BSA and 1 U RNase inhibitor. In both reactions, 0.5 nM double stranded RNA substrate in a final volume of 50 ml was used. The reaction was

20 carried out at 37 °C for 1 h and terminated by an addition of 10 ml of 0.5 M EDTA. The released primer was captured using 60 ml of 100 nM biotinylated capture oligomer (5'-biotin-GCT-CGC-CCG-GGG-ATC-CTC-TAG-3') (Gibco/BRL, Grand Island, NY) (SEQ ID NO: 123) in 2X hybridization buffer (40 mM HEPES [pH 7.3], 2M NaCl, 2 mg/ml BSA) at

25 37 °C for 1 h. The primer-oligomer complex was retained by Streptavidin coated SPA beads (SPA, Amersham Life Science Inc., Arlington Height, IL), filtered and washed thoroughly with wash buffer (20 mM HEPES [pH 7.3], 15 mM NaCl, 1.5 mM sodium citrate and 0.05% SDS). The amount of the released labeled primer was quantified using a

30 TopCount reader (Packard A991200, Meriden, CT).

As shown in Fig. 6, the covalent His-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁ displayed nucleic acid unwinding activity which was proportional to the

- 58 -

concentration of enzyme. In the linear range of the assay for both enzymes (1 - 10 pM), about 5 - 6 fold more product was released by the His-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁ than that from an equivalent concentration of full length His-NS3₁₋₆₃₁/NS4A₁₋₅₄ complex. In addition, 10 fold less covalent His-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁ complex was required to yield a similar percentage of unwound products compared with the full length His-NS3₁₋₆₃₁/NS4A₁₋₅₄ complex in the corresponding reactions.

The nucleic acid unwinding activity associated with the recombinant covalent His-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁ complex is useful for screening inhibitors of this function. For antiviral screening, compounds were tested at concentrations of less than 40 mM in the assay conditions as described above except that 0.3 nM of the double stranded RNA substrate and 20 pM of the covalent His-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁ complex were used in a reaction which was carried out at room temperature for 30 minutes. The inhibition of the enzyme was monitored by a decrease in the level of released labeled primer as reflected in fewer counts in the capture assay. IC₅₀ of the inhibitory compounds was determined as the concentration of the compounds required to inhibit 50% of the unwinding activity.

EXAMPLE 8

Determination of ATPase activity

ATPase activity of the covalent His-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁ complex (SEQ ID NO: 4) was monitored by direct measurement of [α -³²P]ATP hydrolysis using thin layer chromatography. The enzyme was incubated with 1 mM ATP mixed with [α -³²P]ATP (3000 Ci/mmol, approximately 0.5 mCi per reaction) in a reaction buffer containing 50 mM HEPES [pH 7.3], 10 mM KCl, 0.5 mM DTT, 100 mg/ml bovine serum albumin, fraction V (BSA), 1 mM MgCl₂ in the presence or absence of 1 mM polyuridylic acid (poly U) (Pharmacia, Piscataway, NJ) in a final volume of 10 ml. The reaction was carried out at 37 °C for 1 h and terminated by an addition of 1 ml of 0.5 M EDTA. Half a microliter of the reaction mix was spotted onto a polyethyleneimine-cellulose sheet

- 59 -

(SA Scientific Adsorbents Inc., Atlanta, GA) and developed by ascending chromatography in 0.375 M potassium phosphate buffer [pH 3.5]. The cellulose sheet was dried and quantified with a Storm 860 PhosphoImager (Molecular Dynamics, Sunnyvale, CA).

- 5 The covalent His-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁ complex exhibited poly U dependent ATPase activity which was proportional to the concentration of the enzyme. The ATP hydrolysis (8 - 13 fold increase) was enhanced in the presence of poly U at all enzyme concentrations examined (see Figure 7). Only minimal ATP hydrolysis was observed in
- 10 the absence of poly U.

 The presence of ATPase activity in this covalent His-NS4A₂₁₋₃₂-GSGS-NS3₃₋₆₃₁ complex makes it suitable for screening inhibitors against HCV helicase.

- 60 -

WE CLAIM:

1. A covalent HCV NS4A-NS3 complex comprising the central hydrophobic domain of native HCV NS4A peptide, a linker, and
5 the HCV NS3 serine protease domain, wherein the hydrophobic domain of native HCV NS4A peptide is tethered by the linker to the amino terminus of the HCV NS3 protease domain.
2. The covalent HCV NS4A-NS3 complex of claim 1, wherein
10 the linker comprises at least about 4 amino acid residues.
3. The covalent HCV NS4A-NS3 complex of claim 2, wherein the linker consists essentially of 4-6 amino acid residues.
- 15 4. The covalent HCV NS4A-NS3 complex of claim 3, wherein the linker consists essentially of about 4 amino acid residues.
5. The covalent HCV NS4A-NS3 complex of claim 4, wherein the linker has a sequence defined by SEQ ID NO: 21 or SEQ ID NO: 22.
20
6. The covalent HCV NS4A-NS3 complex of claim 5, having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-20.
- 25 7. The covalent HCV NS4A-NS3 complex of claim 1 which is modified by replacement of one or more hydrophobic amino acid residues at position 17 or 18 of the HCV NS3 serine protease domain with a hydrophilic amino acid residue.
- 30 8. The covalent HCV NS4A-NS3 complex of claim 7 in which one or more isoleucine residues at position 17 or 18 of the HCV NS3 serine protease domain is replaced by a lysine residue.

- 61 -

9. The covalent HCV NS4A-NS3 complex of claim 8, having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2-4, 6-8, 10, 12-14 and 16-18.

5 10. The covalent HCV NS4A-NS3 complex of claim 1 which is modified by replacement of a serine residue at position 139 of the HCV NS3 serine protease domain with an alanine residue.

10 11. The covalent HCV NS4A-NS3 complex of claim 10, having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5-8, 15-18 and 20.

15 12. A nucleic acid encoding a covalent HCV NS4A-NS3 complex, which covalent HCV NS4A-NS3 complex comprises the central hydrophobic domain of native HCV NS4A peptide, a linker, and the HCV NS3 serine protease domain, wherein the hydrophobic domain of native HCV NS4A peptide is tethered by the amino acid linker to the amino terminus of the HCV NS3 protease domain.

20 13. The nucleic acid of claim 12, wherein the linker comprises a least about 4 amino acid residues.

25 14. The nucleic acid of claim 13, wherein the linker consists essentially of 4-6 amino acid residues.

15. The nucleic acid of claim 14, wherein the linker consists essentially of 4 amino acid residues.

30 16. The nucleic acid of claim 15, wherein the amino acid linker has a sequence defined by SEQ ID NO: 21 or SEQ ID NO: 22.

- 62 -

17. The nucleic acid of claim 16, which encodes a covalent HCV NS4A-NS3 complex having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-20.

5 18. The nucleic acid of claim 12, which encodes a covalent HCV NS4A-NS3 complex which is modified by replacement of one or more hydrophobic amino acid residues at position 17 or 18 of the HCV NS3 serine protease domain with a hydrophilic amino acid residue.

10 19. The nucleic acid of claim 18 which encodes a covalent HCV NS4A-NS3 complex in which one or more isoleucine residues at position 17 or 18 of the HCV NS3 serine protease domain are replaced by a lysine residue.

15 20. The nucleic acid of claim 19, which encodes a covalent HCV NS4A-NS3 complex having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2-4, 6-8, 10, 12-14 and 16-18.

20 21. The nucleic acid of claim 12, which encodes a covalent HCV NS4A-NS3 complex which is modified by replacement of a serine residue at position 139 of the HCV NS3 serine protease domain with an alanine residue.

25 22. The nucleic acid of claim 21, which encodes a covalent HCV NS4A-NS3 complex having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5-8, 15-18 and 20.

23. A recombinant vector comprising the nucleic acid of claim 12, which vector is capable of directing expression of the nucleic acid.

30

24. A host cell comprising the recombinant vector of claim 23.

- 63 -

25. A method for making a covalent HCV NS4A-NS3 complex comprising culturing the host cell of claim 24 under conditions in which the nucleic acid or vector is expressed.

5 26. A method for identifying an HCV NS3 protease inhibitor, comprising (a) contacting a covalent HCV NS4A-NS3 complex of claim 1 with a peptide substrate and a suspected protease inhibitor under conditions in which proteolysis can occur; and (b) detecting whether the covalent HCV NS4-NS3 complex has cleaved the substrate.

10 27. A method for identifying an inhibitor of the nucleic acid unwinding activity of an HCV NS3 helicase, comprising (a) contacting a covalent HCV NS4A-NS3 complex of SEQ ID NO: 4, 12-19 or 20 with a double stranded RNA substrate and a suspected inhibitor under
15 conditions in which unwinding of the substrate can occur; and (b) detecting whether and the extent to which the covalent HCV NS4-NS3 complex has unwound the substrate.

20 28. A method for identifying an inhibitor of an HCV NS3 helicase, comprising (a) contacting a covalent HCV NS4A-NS3 complex of SEQ ID NO: 4, 12-19 or 20 with ATP and a suspected inhibitor under conditions in which ATP hydrolysis can occur; and (b) detecting whether the covalent HCV NS4-NS3 complex has exhibited ATPase activity.

1/7

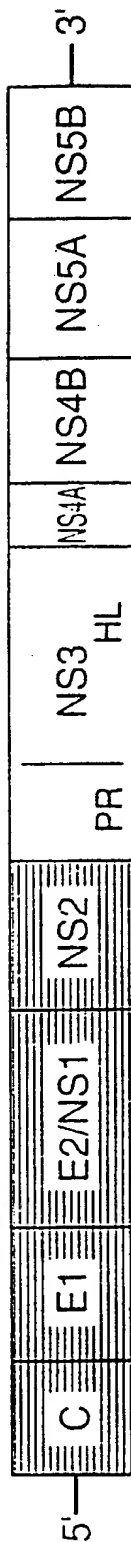


FIG. 1

2/7

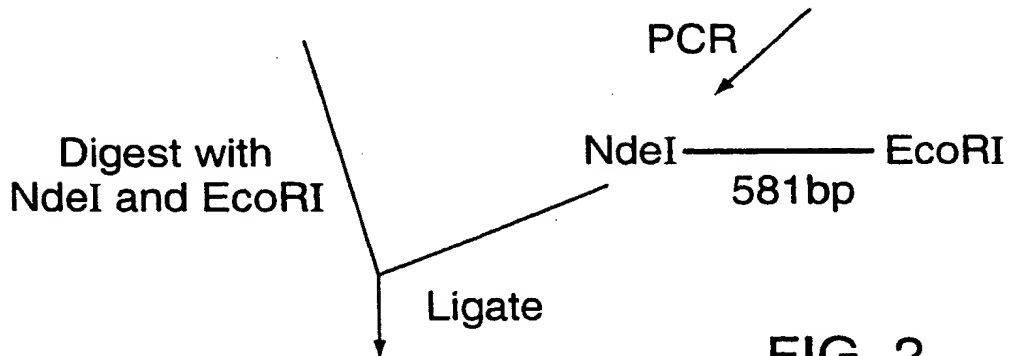
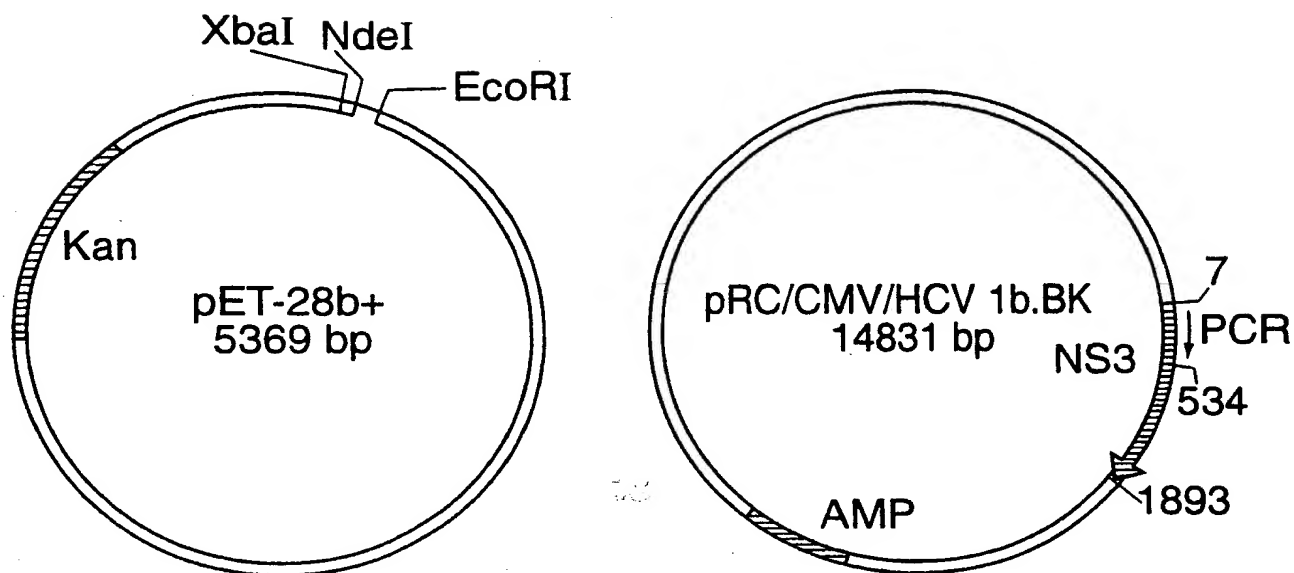
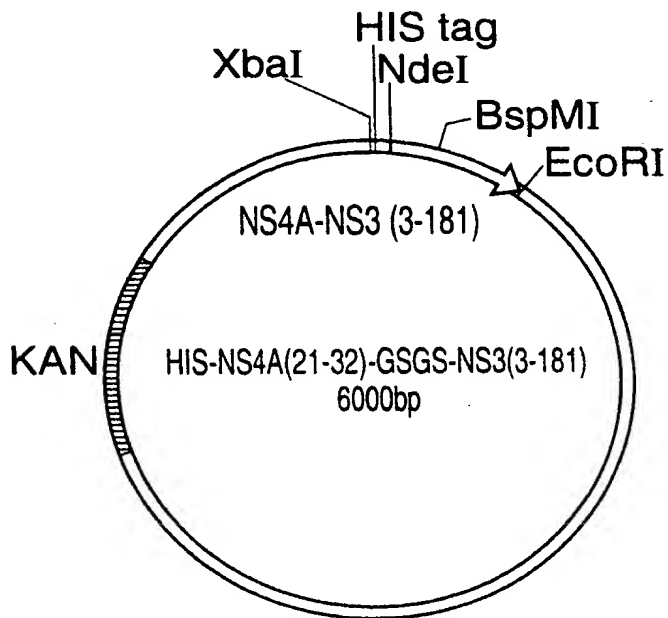


FIG. 2



3/7

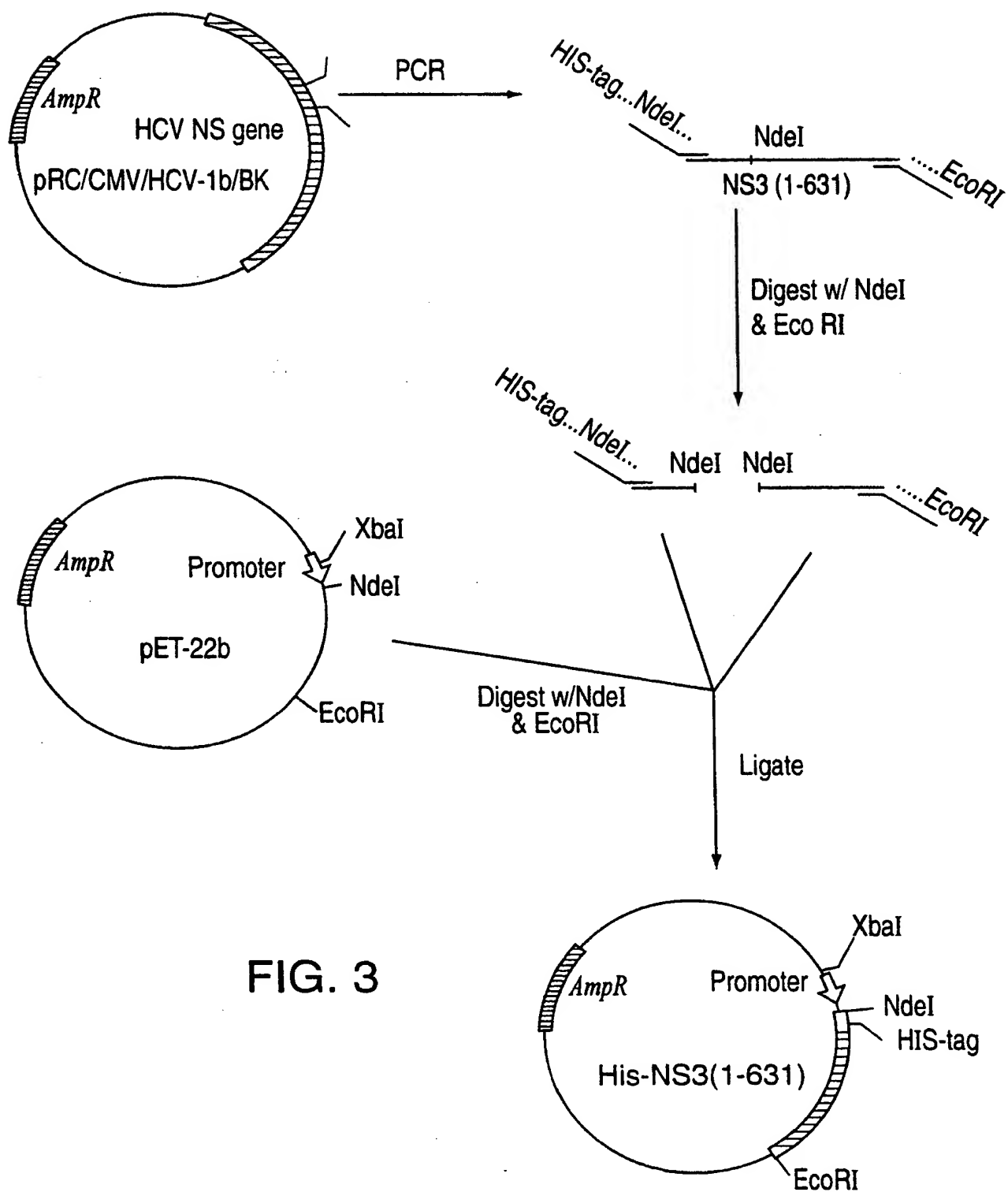


FIG. 3

4/7

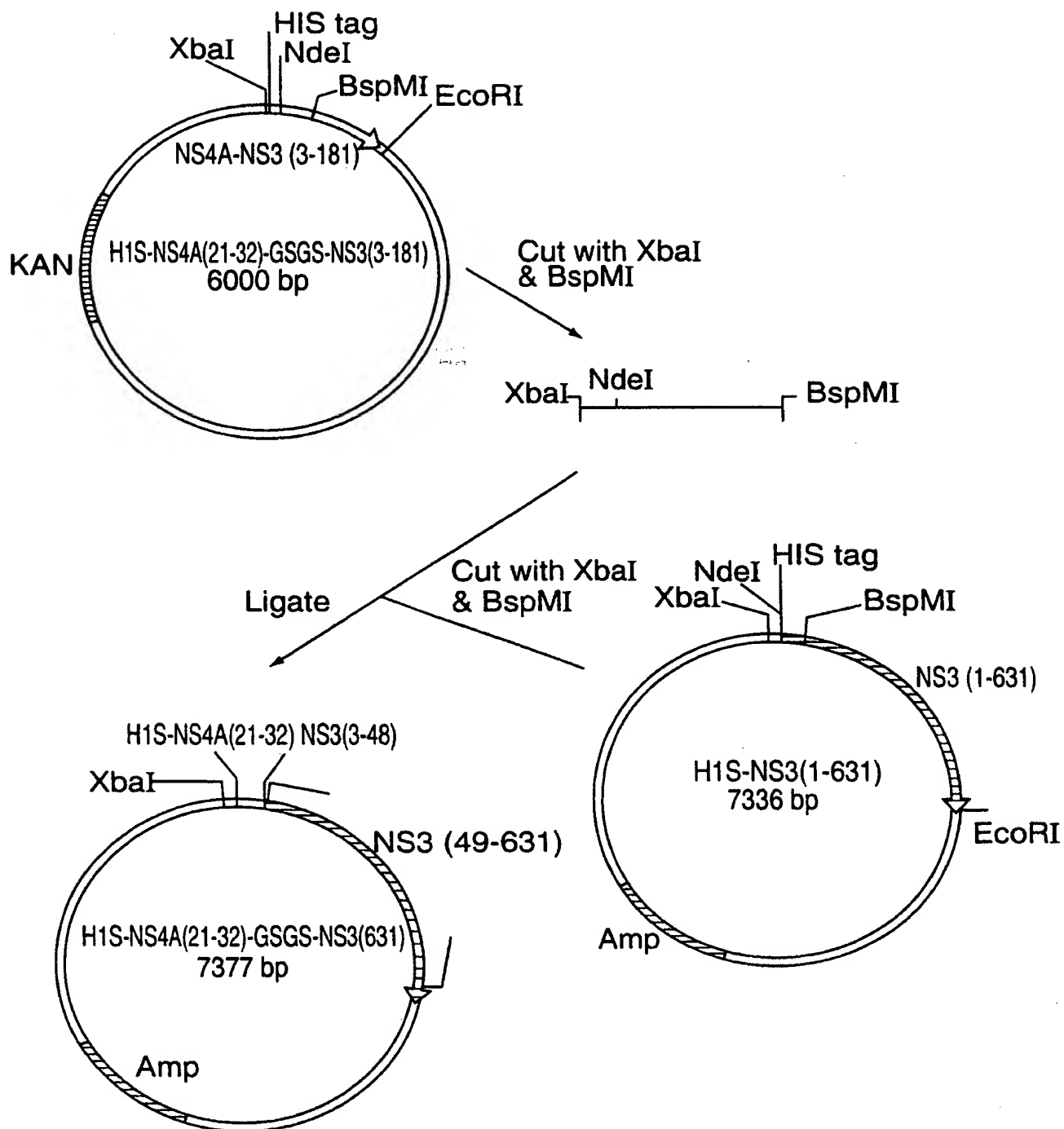


FIG. 4

5/7

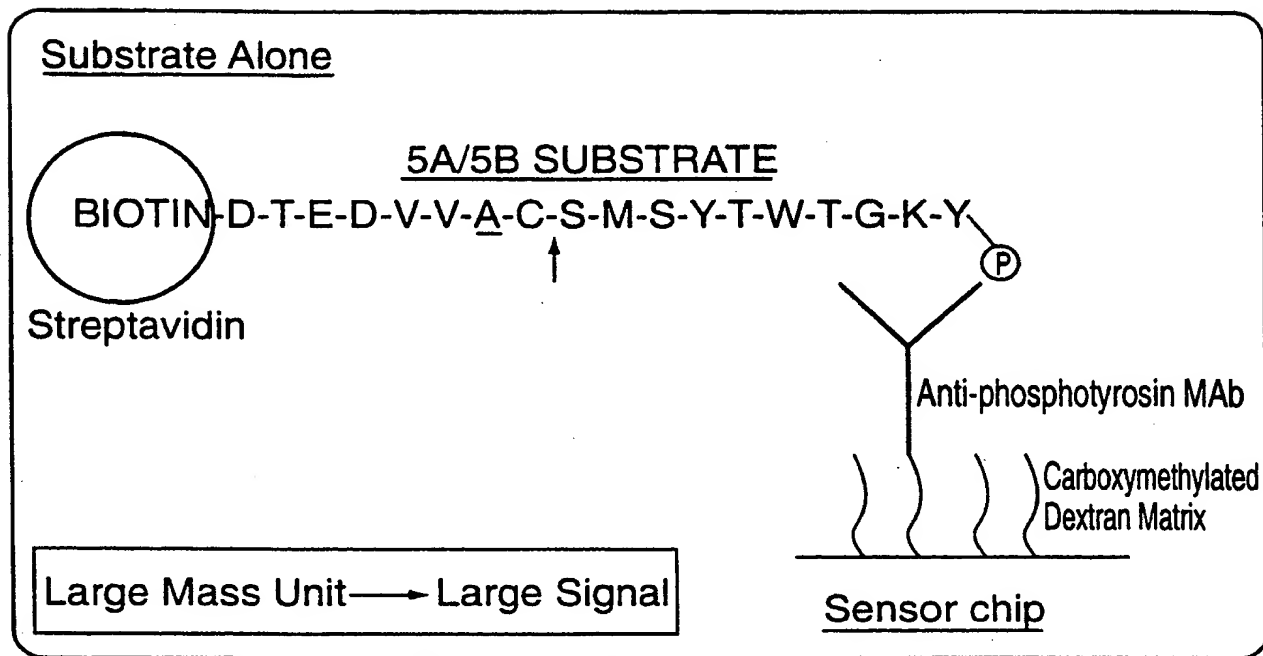


FIG. 5A

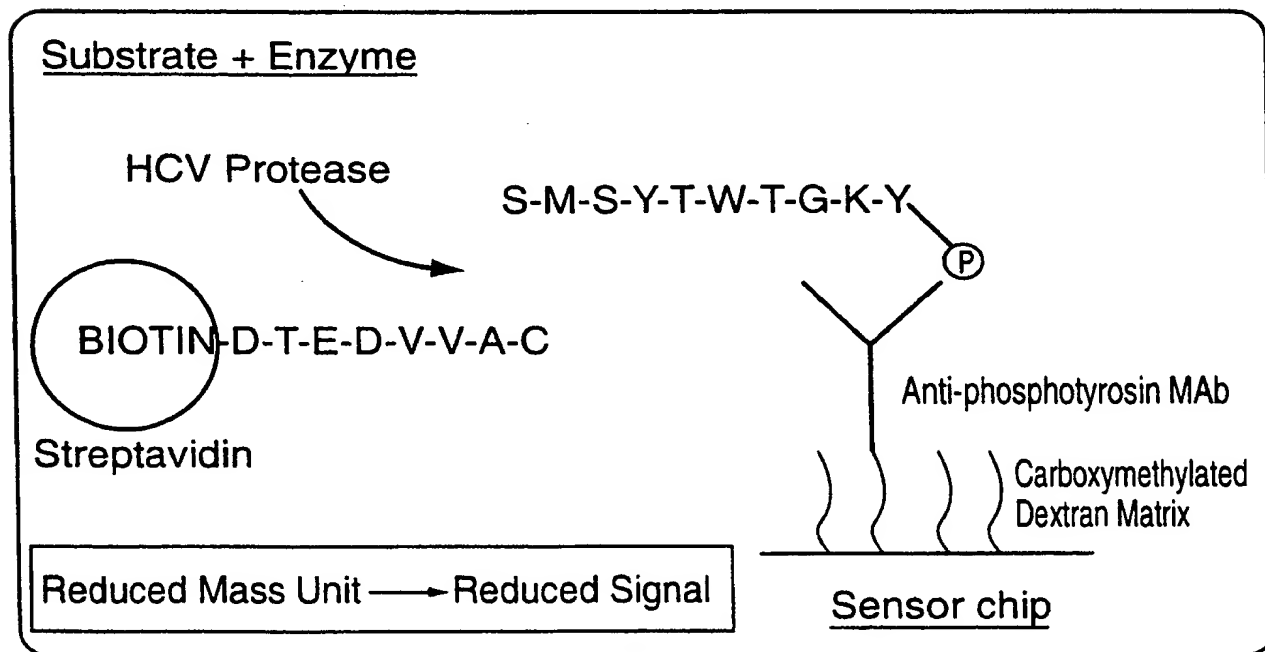


FIG. 5B

6/7

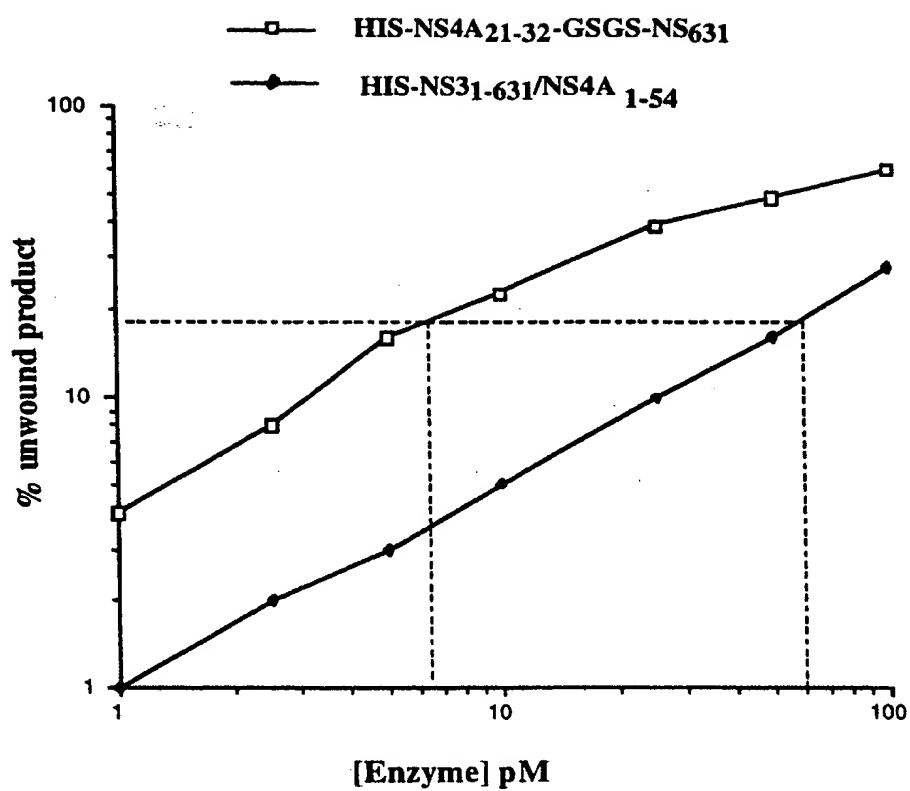


FIG. 6

7/7

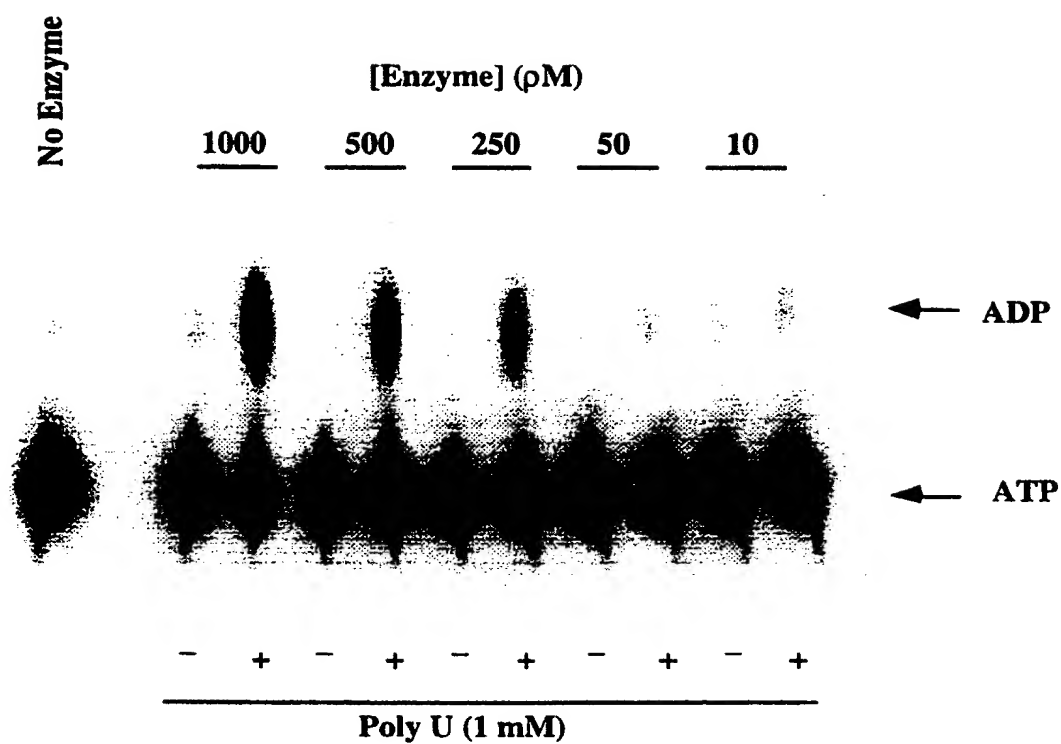


FIG. 7

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:

(A) NAME: Schering Corp.
(B) STREET: 2000 Galloping Hill Road
(C) CITY: Kenilworth
(D) STATE: New Jersey
(E) COUNTRY: USA
(F) ZIP: 07090
(G) TELEPHONE: 908-298-5056
(H) TELEFAX: 908-298-5388

(ii) TITLE OF INVENTION: Covalent Complexes of Hepatitis C Virus
NS3 Protease and NS4A Cofactor Peptide

(iii) NUMBER OF SEQUENCES: 123

(iv) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: Power Macintosh
(C) OPERATING SYSTEM: 8.0.1
(D) SOFTWARE: Microsoft Word 6.0.1

(v) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(vi) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: US 60/067,315
(B) FILING DATE: 28-NOV-1997

(A) APPLICATION NUMBER: US 60/094,331
(B) FILING DATE: 28-JUL-1998

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 217 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Met Gly Ser Ser His His His His His Ser Ser Gly Leu Val Pro
1 5 10 15
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu
20 25 30
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu

SUBSTITUTE SHEET (rule 26)

35	40	45
Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val		
50	55	60
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala		
65	70	75 80
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser		
	85	90 95
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn		
	100	105 110
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser		
	115	120 125
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg		
	130	135 140
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser		
	145	150 155 160
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly		
	165	170 175
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala		
	180	185 190
Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu		
	195	200 205
Ser Met Glu Thr Thr Met Arg Ser *		
	210	215

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 217 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Gly Ser Ser His His His His His Ser Ser Gly Leu Val Pro	
1	5 10 15
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu	
	20 25 30
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu	
	35 40 45
Leu Gly Cys Lys Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val	

50 55 60
 Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala
 65 70 75 80
 Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser
 85 90 95
 Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn
 100 105 110
 Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser
 115 120 125
 Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg
 130 135 140
 His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser
 145 150 155 160
 Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly
 165 170 175
 Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala
 180 185 190
 Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu
 195 200 205
 Ser Met Glu Thr Thr Met Arg Ser *
 210 215

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 217 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro
 1 5 10 15
 Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu
 20 25 30
 Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu
 35 40 45
 Leu Gly Cys Ile Lys Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val
 50 55 60
 Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala

65		70		75		80
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser	85		90		95	
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn	100		105		110	
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser	115		120		125	
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg	130		135		140	
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser	145		150		155	160
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly	165		170		175	
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala	180		185		190	
Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu	195		200		205	
Ser Met Glu Thr Thr Met Arg Ser *	210		215			

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 217 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Gly Ser Ser His His His His His Ser Ser Gly Leu Val Pro	1	5	10	15
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu	20	25	30	
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu	35	40	45	
Leu Gly Cys Lys Lys Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val	50	55	60	
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala	65	70	75	80
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser				

SUBSTITUTE SHEET (rule 26)

	85		90		95
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn					
	100		105		110
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser					
	115		120		125
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg					
	130		135		140
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser					
	145		150		155
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly					
	165		170		175
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala					
	180		185		190
Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu					
	195		200		205
Ser Met Glu Thr Thr Met Arg Ser *					
	210		215		

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 216 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro					
1		5		10	15
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu					
	20		25		30
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu					
	35		40		45
Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val					
	50		55		60
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala					
	65		70		75
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser					
	85		90		95
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn					

100	105	110
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser		
115	120	125
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg		
130	135	140
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser		
145	150	155
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ala Gly Gly		
	165	170
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala		
	180	185
Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu		
195	200	205
Ser Met Glu Thr Thr Met Arg Ser		
210	215	

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 216 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Met Gly Ser Ser His His His His His Ser Ser Gly Leu Val Pro		
1	5	10
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu		
20	25	30
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu		
35	40	45
Leu Gly Cys Lys Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val		
50	55	60
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala		
65	70	75
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser		
	85	90
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn		
100	105	110
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser		

SUBSTITUTE SHEET (rule 26)

115	120	125
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg		
130	135	140
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser		
145	150	155
		160
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ala Gly Gly		
	165	170
		175
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala		
	180	185
		190
Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu		
	195	200
		205
Ser Met Glu Thr Thr Met Arg Ser		
210	215	

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 217 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro		
1	5	10
		15
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu		
	20	25
		30
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu		
	35	40
		45
Leu Gly Cys Ile Lys Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val		
	50	55
		60
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala		
	65	70
		75
		80
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser		
	85	90
		95
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn		
	100	105
		110
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser		
	115	120
		125
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg		

SUBSTITUTE SHEET (rule 26)

130		135		140
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser				
145		150		155
				160
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ala Gly Gly				
	165		170	175
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala				
	180		185	190
Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu				
	195		200	205
Ser Met Glu Thr Thr Met Arg Ser *				
210		215		

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 217 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro				
1		5		10
				15
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu				
	20		25	30
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu				
	35		40	45
Leu Gly Cys Lys Lys Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val				
	50		55	60
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala				
	65		70	75
				80
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser				
	85		90	95
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn				
	100		105	110
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser				
	115		120	125
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg				
	130		135	140
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser				

SUBSTITUTE SHEET (rule 26)

```

145              150              155              160
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ala Gly Gly
              165              170              175
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala
              180              185              190
Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu
              195              200              205
Ser Met Glu Thr Thr Met Arg Ser *
              210              215

```

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 217 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

```

Met Gly Ser Ser His His His His His Ser Ser Gly Leu Val Pro
 1              5              10              15
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu
              20              25              30
Ser Pro Ala Gly Gly Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu
              35              40              45
Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val
              50              55              60
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala
              65              70              75              80
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser
              85              90              95
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn
              100              105              110
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser
              115              120              125
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg
              130              135              140
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser
              145              150              155              160

```

SUBSTITUTE SHEET (rule 26)

```

Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly
      165                      170                      175

Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala
      180                      185                      190

Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu
      195                      200                      205

Ser Met Glu Thr Thr Met Arg Ser *
      210                      215

```

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 217 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```

Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro
 1              5              10              15

Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu
      20              25              30

Ser Pro Ala Gly Gly Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu
      35              40              45

Leu Gly Cys Lys Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val
      50              55              60

Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala
      65              70              75              80

Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser
      85              90              95

Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn
      100             105             110

Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser
      115             120             125

Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg
      130             135             140

His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser
      145             150             155             160

Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly
      165             170             175

```

Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala
 180 185 190

Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu
 195 200 205

Ser Met Glu Thr Thr Met Arg Ser *
 210 215

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 665 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro
 1 5 10 15

Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu
 20 25 30

Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu
 35 40 45

Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val
 50 55 60

Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala
 65 70 75 80

Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser
 85 90 95

Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn
 100 105 110

Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser
 115 120 125

Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg
 130 135 140

His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser
 145 150 155 160

Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly
 165 170 175

Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala
 180 185 190

Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu
 195 200 205
 Ser Met Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser
 210 215 220
 Pro Pro Ala Val Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro
 225 230 235 240
 Thr Gly Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln
 245 250 255
 Gly Tyr Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly
 260 265 270
 Phe Gly Ala Tyr Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg
 275 280 285
 Thr Gly Val Arg Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr
 290 295 300
 Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp
 305 310 315 320
 Ile Ile Ile Cys Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu
 325 330 335
 Gly Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu
 340 345 350
 Val Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His
 355 360 365
 Pro Asn Ile Glu Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe
 370 375 380
 Tyr Gly Lys Ala Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu
 385 390 395 400
 Ile Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu
 405 410 415
 Ser Gly Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val
 420 425 430
 Ser Val Ile Pro Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala
 435 440 445
 Leu Met Thr Gly Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn
 450 455 460
 Thr Cys Val Thr Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr
 465 470 475 480
 Ile Glu Thr Thr Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg
 485 490 495
 Arg Gly Arg Thr Gly Arg Gly Arg Arg Gly Ile Tyr Arg Phe Val Thr

SUBSTITUTE SHEET (rule 26)

500	505	510
Pro Gly Glu Arg Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu		
515	520	525
Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr		
530	535	540
Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys		
545	550	555
Gln Asp His Leu Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His		
565	570	575
Ile Asp Ala His Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe		
580	585	590
Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala		
595	600	605
Pro Pro Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys		
610	615	620
Pro Thr Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val		
625	630	635
Gln Asn Glu Val Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala		
645	650	655
Cys Met Ser Ala Asp Leu Glu Val Val		
660	665	

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 665 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Met Gly Ser Ser His His His His His Ser Ser Gly Leu Val Pro	
1 5 10 15	
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu	
20 25 30	
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu	
35 40 45	
Leu Gly Cys Lys Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val	
50 55 60	
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala	

65		70		75		80
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser	85		90		95	
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn	100		105		110	
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser	115		120		125	
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg	130		135		140	
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser	145		150		155	160
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly		165		170		175
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala		180		185		190
Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu		195		200		205
Ser Met Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser		210		215		220
Pro Pro Ala Val Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro		225		230		235
Thr Gly Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln		245		250		255
Gly Tyr Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly		260		265		270
Phe Gly Ala Tyr Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg		275		280		285
Thr Gly Val Arg Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr		290		295		300
Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp		305		310		315
Ile Ile Ile Cys Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu		325		330		335
Gly Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu		340		345		350
Val Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His		355		360		365
Pro Asn Ile Glu Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe		370		375		380

Tyr Gly Lys Ala Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu
 385 390 395 400
 Ile Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu
 405 410 415
 Ser Gly Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val
 420 425 430
 Ser Val Ile Pro Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala
 435 440 445
 Leu Met Thr Gly Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn
 450 455 460
 Thr Cys Val Thr Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr
 465 470 475 480
 Ile Glu Thr Thr Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg
 485 490 495
 Arg Gly Arg Thr Gly Arg Gly Arg Arg Gly Ile Tyr Arg Phe Val Thr
 500 505 510
 Pro Gly Glu Arg Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu
 515 520 525
 Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr
 530 535 540
 Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys
 545 550 555 560
 Gln Asp His Leu Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His
 565 570 575
 Ile Asp Ala His Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe
 580 585 590
 Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala
 595 600 605
 Pro Pro Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys
 610 615 620
 Pro Thr Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val
 625 630 635 640
 Gln Asn Glu Val Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala
 645 650 655
 Cys Met Ser Ala Asp Leu Glu Val Val
 660 665

(2) INFORMATION FOR SEQ ID NO:13:

SUBSTITUTE SHEET (rule 26)

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 665 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```

Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro
 1             5             10             15
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu
 20             25             30
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu
 35             40             45
Leu Gly Cys Ile Lys Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val
 50             55             60
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala
 65             70             75             80
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser
 85             90             95
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn
100            105            110
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser
115            120            125
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg
130            135            140
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser
145            150            155            160
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly
165            170            175
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala
180            185            190
Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu
195            200            205
Ser Met Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser
210            215            220
Pro Pro Ala Val Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro
225            230            235            240
Thr Gly Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln
245            250            255

```

SUBSTITUTE SHEET (rule 26)

Gly Tyr Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly
 260 265 270
 Phe Gly Ala Tyr Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg
 275 280 285
 Thr Gly Val Arg Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr
 290 295 300
 Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp
 305 310 315 320
 Ile Ile Ile Cys Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu
 325 330 335
 Gly Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu
 340 345 350
 Val Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His
 355 360 365
 Pro Asn Ile Glu Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe
 370 375 380
 Tyr Gly Lys Ala Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu
 385 390 395 400
 Ile Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu
 405 410 415
 Ser Gly Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val
 420 425 430
 Ser Val Ile Pro Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala
 435 440 445
 Leu Met Thr Gly Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn
 450 455 460
 Thr Cys Val Thr Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr
 465 470 475 480
 Ile Glu Thr Thr Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg
 485 490 495
 Arg Gly Arg Thr Gly Arg Gly Arg Arg Gly Ile Tyr Arg Phe Val Thr
 500 505 510
 Pro Gly Glu Arg Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu
 515 520 525
 Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr
 530 535 540
 Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys
 545 550 555 560
 Gln Asp His Leu Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His

SUBSTITUTE SHEET (rule 26)

[illegible]

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 665 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Met	Gly	Ser	Ser	His	His	His	His	His	Ser	Ser	Gly	Leu	Val	Pro	
1				5					10				15		
Arg	Gly	Ser	His	Met	Gly	Ser	Val	Val	Ile	Val	Gly	Arg	Ile	Ile	Leu
			20					25					30		
Ser	Gly	Ser	Gly	Ser	Ile	Thr	Ala	Tyr	Ser	Gln	Gln	Thr	Arg	Gly	Leu
		35					40					45			
Leu	Gly	Cys	Lys	Lys	Thr	Ser	Leu	Thr	Gly	Arg	Asp	Lys	Asn	Gln	Val
	50					55					60				
Glu	Gly	Glu	Val	Gln	Val	Val	Ser	Thr	Ala	Thr	Gln	Ser	Phe	Leu	Ala
65					70					75					80
Thr	Cys	Val	Asn	Gly	Val	Cys	Trp	Thr	Val	Tyr	His	Gly	Ala	Gly	Ser
				85					90					95	
Lys	Thr	Leu	Ala	Gly	Pro	Lys	Gly	Pro	Ile	Thr	Gln	Met	Tyr	Thr	Asn
			100					105					110		
Val	Asp	Gln	Asp	Leu	Val	Gly	Trp	Gln	Ala	Pro	Pro	Gly	Ala	Arg	Ser
		115					120					125			
Leu	Thr	Pro	Cys	Thr	Cys	Gly	Ser	Ser	Asp	Leu	Tyr	Leu	Val	Thr	Arg

130	135	140
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser		
145	150	155 160
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly		
	165	170 175
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala		
	180	185 190
Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu		
	195	200 205
Ser Met Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser		
	210	215 220
Pro Pro Ala Val Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro		
	225	230 235 240
Thr Gly Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln		
	245	250 255
Gly Tyr Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly		
	260	265 270
Phe Gly Ala Tyr Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg		
	275	280 285
Thr Gly Val Arg Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr		
	290	295 300
Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp		
	305	310 315 320
Ile Ile Ile Cys Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu		
	325	330 335
Gly Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu		
	340	345 350
Val Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His		
	355	360 365
Pro Asn Ile Glu Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe		
	370	375 380
Tyr Gly Lys Ala Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu		
	385	390 395 400
Ile Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu		
	405	410 415
Ser Gly Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val		
	420	425 430
Ser Val Ile Pro Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala		
	435	440 445

SUBSTITUTE SHEET (rule 26)

Leu Met Thr Gly Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn
 450 455 460
 Thr Cys Val Thr Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr
 465 470 475 480
 Ile Glu Thr Thr Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg
 485 490 495
 Arg Gly Arg Thr Gly Arg Gly Arg Arg Gly Ile Tyr Arg Phe Val Thr
 500 505 510
 Pro Gly Glu Arg Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu
 515 520 525
 Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr
 530 535 540
 Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys
 545 550 555 560
 Gln Asp His Leu Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His
 565 570 575
 Ile Asp Ala His Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe
 580 585 590
 Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala
 595 600 605
 Pro Pro Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys
 610 615 620
 Pro Thr Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val
 625 630 635 640
 Gln Asn Glu Val Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala
 645 650 655
 Cys Met Ser Ala Asp Leu Glu Val Val
 660 665

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 665 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro
 1 5 10 15

Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu
 20 25 30
 Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu
 35 40 45
 Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val
 50 55 60
 Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala
 65 70 75 80
 Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser
 85 90 95
 Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn
 100 105 110
 Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser
 115 120 125
 Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg
 130 135 140
 His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser
 145 150 155 160
 Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ala Gly Gly
 165 170 175
 Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala
 180 185 190
 Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu
 195 200 205
 Ser Met Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser
 210 215 220
 Pro Pro Ala Val Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro
 225 230 235 240
 Thr Gly Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln
 245 250 255
 Gly Tyr Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly
 260 265 270
 Phe Gly Ala Tyr Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg
 275 280 285
 Thr Gly Val Arg Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr
 290 295 300
 Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp
 305 310 315 320

SUBSTITUTE SHEET (rule 26)

Ile Ile Ile Cys Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu
 325 330 335
 Gly Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu
 340 345 350
 Val Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His
 355 360 365
 Pro Asn Ile Glu Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe
 370 375 380
 Tyr Gly Lys Ala Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu
 385 390 395 400
 Ile Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu
 405 410 415
 Ser Gly Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val
 420 425 430
 Ser Val Ile Pro Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala
 435 440 445
 Leu Met Thr Gly Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn
 450 455 460
 Thr Cys Val Thr Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr
 465 470 475 480
 Ile Glu Thr Thr Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg
 485 490 495
 Arg Gly Arg Thr Gly Arg Gly Arg Arg Gly Ile Tyr Arg Phe Val Thr
 500 505 510
 Pro Gly Glu Arg Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu
 515 520 525
 Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr
 530 535 540
 Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys
 545 550 555 560
 Gln Asp His Leu Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His
 565 570 575
 Ile Asp Ala His Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe
 580 585 590
 Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala
 595 600 605
 Pro Pro Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys
 610 615 620
 Pro Thr Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val

625	630	635	640
Gln Asn Glu Val Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala			
	645	650	655
Cys Met Ser Ala Asp Leu Glu Val Val			
	660	665	

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 665 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro			
1	5	10	15
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu			
	20	25	30
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu			
	35	40	45
Leu Gly Cys Lys Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val			
	50	55	60
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala			
	65	70	75
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser			
	85	90	95
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn			
	100	105	110
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser			
	115	120	125
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg			
	130	135	140
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser			
	145	150	155
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ala Gly Gly			
	165	170	175
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala			
	180	185	190
Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu			

SUBSTITUTE SHEET (rule 26)

195					200					205					
Ser	Met	Glu	Thr	Thr	Met	Arg	Ser	Pro	Val	Phe	Thr	Asp	Asn	Ser	Ser
210					215					220					
Pro	Pro	Ala	Val	Pro	Gln	Ser	Phe	Gln	Val	Ala	His	Leu	His	Ala	Pro
225					230					235					240
Thr	Gly	Ser	Gly	Lys	Ser	Thr	Lys	Val	Pro	Ala	Ala	Tyr	Ala	Ala	Gln
				245					250					255	
Gly	Tyr	Lys	Val	Leu	Val	Leu	Asn	Pro	Ser	Val	Ala	Ala	Thr	Leu	Gly
			260					265					270		
Phe	Gly	Ala	Tyr	Met	Ser	Lys	Ala	His	Gly	Ile	Asp	Pro	Asn	Ile	Arg
		275					280					285			
Thr	Gly	Val	Arg	Thr	Ile	Thr	Thr	Gly	Ala	Pro	Val	Thr	Tyr	Ser	Thr
		290					295					300			
Tyr	Gly	Lys	Phe	Leu	Ala	Asp	Gly	Gly	Cys	Ser	Gly	Gly	Ala	Tyr	Asp
305					310					315					320
Ile	Ile	Ile	Cys	Asp	Glu	Cys	His	Ser	Thr	Asp	Ser	Thr	Thr	Ile	Leu
				325					330					335	
Gly	Ile	Gly	Thr	Val	Leu	Asp	Gln	Ala	Glu	Thr	Ala	Gly	Ala	Arg	Leu
			340					345					350		
Val	Val	Leu	Ala	Thr	Ala	Thr	Pro	Pro	Gly	Ser	Val	Thr	Val	Pro	His
		355					360					365			
Pro	Asn	Ile	Glu	Glu	Val	Ala	Leu	Ser	Asn	Thr	Gly	Glu	Ile	Pro	Phe
		370					375					380			
Tyr	Gly	Lys	Ala	Ile	Pro	Ile	Glu	Ala	Ile	Arg	Gly	Gly	Arg	His	Leu
385					390					395					400
Ile	Phe	Cys	His	Ser	Lys	Lys	Lys	Cys	Asp	Glu	Leu	Ala	Ala	Lys	Leu
				405					410					415	
Ser	Gly	Leu	Gly	Ile	Asn	Ala	Val	Ala	Tyr	Tyr	Arg	Gly	Leu	Asp	Val
			420					425					430		
Ser	Val	Ile	Pro	Thr	Ile	Gly	Asp	Val	Val	Val	Val	Ala	Thr	Asp	Ala
		435					440					445			
Leu	Met	Thr	Gly	Tyr	Thr	Gly	Asp	Phe	Asp	Ser	Val	Ile	Asp	Cys	Asn
				450			455					460			
Thr	Cys	Val	Thr	Gln	Thr	Val	Asp	Phe	Ser	Leu	Asp	Pro	Thr	Phe	Thr
465					470					475					480
Ile	Glu	Thr	Thr	Thr	Val	Pro	Gln	Asp	Ala	Val	Ser	Arg	Ser	Gln	Arg
				485					490					495	
Arg	Gly	Arg	Thr	Gly	Arg	Gly	Arg	Arg	Gly	Ile	Tyr	Arg	Phe	Val	Thr
			500				505						510		

SUBSTITUTE SHEET (rule 26)

Pro Gly Glu Arg Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu
 515 520 525

Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr
 530 535 540

Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys
 545 550 555 560

Gln Asp His Leu Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His
 565 570 575

Ile Asp Ala His Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe
 580 585 590

Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala
 595 600 605

Pro Pro Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys
 610 615 620

Pro Thr Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val
 625 630 635 640

Gln Asn Glu Val Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala
 645 650 655

Cys Met Ser Ala Asp Leu Glu Val Val
 660 665

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 665 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Met Gly Ser Ser His His His His His Ser Ser Gly Leu Val Pro
 1 5 10 15

Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu
 20 25 30

Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu
 35 40 45

Leu Gly Cys Ile Lys Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val
 50 55 60

Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala
 65 70 75 80

Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser
 85 90 95
 Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn
 100 105 110
 Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser
 115 120 125
 Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg
 130 135 140
 His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser
 145 150 155 160
 Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ala Gly Gly
 165 170 175
 Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala
 180 185 190
 Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu
 195 200 205
 Ser Met Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser
 210 215 220
 Pro Pro Ala Val Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro
 225 230 235 240
 Thr Gly Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln
 245 250 255
 Gly Tyr Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly
 260 265 270
 Phe Gly Ala Tyr Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg
 275 280 285
 Thr Gly Val Arg Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr
 290 295 300
 Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp
 305 310 315 320
 Ile Ile Ile Cys Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu
 325 330 335
 Gly Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu
 340 345 350
 Val Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His
 355 360 365
 Pro Asn Ile Glu Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe
 370 375 380

SUBSTITUTE SHEET (rule 26)

Tyr Gly Lys Ala Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu
 385 390 395 400
 Ile Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu
 405 410 415
 Ser Gly Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val
 420 425 430
 Ser Val Ile Pro Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala
 435 440 445
 Leu Met Thr Gly Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn
 450 455 460
 Thr Cys Val Thr Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr
 465 470 475 480
 Ile Glu Thr Thr Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg
 485 490 495
 Arg Gly Arg Thr Gly Arg Gly Arg Arg Gly Ile Tyr Arg Phe Val Thr
 500 505 510
 Pro Gly Glu Arg Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu
 515 520 525
 Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr
 530 535 540
 Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys
 545 550 555 560
 Gln Asp His Leu Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His
 565 570 575
 Ile Asp Ala His Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe
 580 585 590
 Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala
 595 600 605
 Pro Pro Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys
 610 615 620
 Pro Thr Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val
 625 630 635 640
 Gln Asn Glu Val Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala
 645 650 655
 Cys Met Ser Ala Asp Leu Glu Val Val
 660 665

(2) INFORMATION FOR SEQ ID NO:18:

SUBSTITUTE SHEET (rule 26)

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 665 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```

Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro
 1              5              10              15
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu
          20              25              30
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu
          35              40              45
Leu Gly Cys Lys Lys Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val
          50              55              60
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala
          65              70              75              80
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser
          85              90              95
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn
          100             105             110
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser
          115             120             125
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg
          130             135             140
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser
          145             150             155             160
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ala Gly Gly
          165             170             175
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala
          180             185             190
Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu
          195             200             205
Ser Met Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser
          210             215             220
Pro Pro Ala Val Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro
          225             230             235             240
Thr Gly Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln
          245             250             255
Gly Tyr Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly

```

SUBSTITUTE SHEET (rule 26)

260	265	270
Phe Gly Ala Tyr Met Ser Lys	Ala His Gly Ile Asp Pro Asn Ile Arg	
275	280	285
Thr Gly Val Arg Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr		
290	295	300
Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp		
305	310	315
Ile Ile Ile Cys Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu		
	325	330
Gly Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu		
	340	345
Val Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His		
	355	360
Pro Asn Ile Glu Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe		
	370	375
Tyr Gly Lys Ala Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu		
	385	390
Ile Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu		
	405	410
Ser Gly Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val		
	420	425
Ser Val Ile Pro Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala		
	435	440
Leu Met Thr Gly Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn		
	450	455
Thr Cys Val Thr Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr		
	465	470
Ile Glu Thr Thr Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg		
	485	490
Arg Gly Arg Thr Gly Arg Gly Arg Arg Gly Ile Tyr Arg Phe Val Thr		
	500	505
Pro Gly Glu Arg Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu		
	515	520
Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr		
	530	535
Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys		
	545	550
Gln Asp His Leu Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His		
	565	570

SUBSTITUTE SHEET (rule 26)

Ile Asp Ala His Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe
 580 585 590

Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala
 595 600 605

Pro Pro Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys
 610 615 620

Pro Thr Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val
 625 630 635 640

Gln Asn Glu Val Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala
 645 650 655

Cys Met Ser Ala Asp Leu Glu Val Val
 660 665

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 671 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro
 1 5 10 15

Arg Gly Ser His Met Ala Tyr Ser Leu Thr Thr Gly Ser Val Val Ile
 20 25 30

Val Gly Arg Ile Ile Leu Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser
 35 40 45

Gln Gln Thr Arg Gly Leu Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly
 50 55 60

Arg Asp Lys Asn Gln Val Glu Gly Glu Val Gln Val Val Ser Thr Ala
 65 70 75 80

Thr Gln Ser Phe Leu Ala Thr Cys Val Asn Gly Val Cys Trp Thr Val
 85 90 95

Tyr His Gly Ala Gly Ser Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile
 100 105 110

Thr Gln Met Tyr Thr Asn Val Asp Gln Asp Leu Val Gly Trp Gln Ala
 115 120 125

Pro Pro Gly Ala Arg Ser Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp
 130 135 140

SUBSTITUTE SHEET (rule 26)

Leu Tyr Leu Val Thr Arg His Ala Asp Val Ile Pro Val Arg Arg Arg
 145 150 155 160
 Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu
 165 170 175
 Lys Gly Ser Ser Gly Gly Pro Leu Leu Cys Pro Ser Gly His Ala Val
 180 185 190
 Gly Ile Phe Arg Ala Ala Val Cys Thr Arg Gly Val Ala Lys Ala Val
 195 200 205
 Asp Phe Val Pro Val Glu Ser Met Glu Thr Thr Met Arg Ser Pro Val
 210 215 220
 Phe Thr Asp Asn Ser Ser Pro Pro Ala Val Pro Gln Ser Phe Gln Val
 225 230 235 240
 Ala His Leu His Ala Pro Thr Gly Ser Gly Lys Ser Thr Lys Val Pro
 245 250 255
 Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val Leu Val Leu Asn Pro Ser
 260 265 270
 Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His Gly
 275 280 285
 Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly Ala
 290 295 300
 Pro Val Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys
 305 310 315 320
 Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser Thr
 325 330 335
 Asp Ser Thr Thr Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala Glu
 340 345 350
 Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro Gly
 355 360 365
 Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser Asn
 370 375 380
 Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Ile Glu Ala Ile
 385 390 395 400
 Arg Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys Asp
 405 410 415
 Glu Leu Ala Ala Lys Leu Ser Gly Leu Gly Ile Asn Ala Val Ala Tyr
 420 425 430
 Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ile Gly Asp Val Val
 435 440 445

SUBSTITUTE SHEET (rule 26)

Val Val Ala Thr Asp Ala Leu Met Thr Gly Tyr Thr Gly Asp Phe Asp
 450 455 460

Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe Ser
 465 470 475 480

Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr Thr Val Pro Gln Asp Ala
 485 490 495

Val Ser Arg Ser Gln Arg Arg Gly Arg Thr Gly Arg Gly Arg Arg Gly
 500 505 510

Ile Tyr Arg Phe Val Thr Pro Gly Glu Arg Pro Ser Gly Met Phe Asp
 515 520 525

Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu
 530 535 540

Leu Thr Pro Ala Glu Thr Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr
 545 550 555 560

Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Ser Val
 565 570 575

Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr Lys
 580 585 590

Gln Ala Gly Asp Asn Phe Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val
 595 600 605

Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp Lys
 610 615 620

Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu Leu
 625 630 635 640

Tyr Arg Leu Gly Ala Val Gln Asn Glu Val Thr Leu Thr His Pro Ile
 645 650 655

Thr Lys Tyr Ile Met Ala Cys Met Ser Ala Asp Leu Glu Val Val
 660 665 670

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 671 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro
 1 5 10 15

Arg Gly Ser His Met Ala Tyr Ser Leu Thr Thr Gly Ser Val Val Ile
 20 25 30

Val Gly Arg Ile Ile Leu Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser
 35 40 45

Gln Gln Thr Arg Gly Leu Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly
 50 55 60

Arg Asp Lys Asn Gln Val Glu Gly Glu Val Gln Val Val Ser Thr Ala
 65 70 75 80

Thr Gln Ser Phe Leu Ala Thr Cys Val Asn Gly Val Cys Trp Thr Val
 85 90 95

Tyr His Gly Ala Gly Ser Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile
 100 105 110

Thr Gln Met Tyr Thr Asn Val Asp Gln Asp Leu Val Gly Trp Gln Ala
 115 120 125

Pro Pro Gly Ala Arg Ser Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp
 130 135 140

Leu Tyr Leu Val Thr Arg His Ala Asp Val Ile Pro Val Arg Arg Arg
 145 150 155 160

Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu
 165 170 175

Lys Gly Ser Ala Gly Gly Pro Leu Leu Cys Pro Ser Gly His Ala Val
 180 185 190

Gly Ile Phe Arg Ala Ala Val Cys Thr Arg Gly Val Ala Lys Ala Val
 195 200 205

Asp Phe Val Pro Val Glu Ser Met Glu Thr Thr Met Arg Ser Pro Val
 210 215 220

Phe Thr Asp Asn Ser Ser Pro Pro Ala Val Pro Gln Ser Phe Gln Val
 225 230 235 240

Ala His Leu His Ala Pro Thr Gly Ser Gly Lys Ser Thr Lys Val Pro
 245 250 255

Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val Leu Val Leu Asn Pro Ser
 260 265 270

Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His Gly
 275 280 285

Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly Ala
 290 295 300

Pro Val Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys
 305 310 315 320

Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser Thr

325	330	335
Asp Ser Thr Thr Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala Glu		
340	345	350
Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro Gly		
355	360	365
Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser Asn		
370	375	380
Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Ile Glu Ala Ile		
385	390	400
Arg Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys Asp		
405	410	415
Glu Leu Ala Ala Lys Leu Ser Gly Leu Gly Ile Asn Ala Val Ala Tyr		
420	425	430
Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ile Gly Asp Val Val		
435	440	445
Val Val Ala Thr Asp Ala Leu Met Thr Gly Tyr Thr Gly Asp Phe Asp		
450	455	460
Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe Ser		
465	470	480
Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr Thr Val Pro Gln Asp Ala		
485	490	495
Val Ser Arg Ser Gln Arg Arg Gly Arg Thr Gly Arg Gly Arg Arg Gly		
500	505	510
Ile Tyr Arg Phe Val Thr Pro Gly Glu Arg Pro Ser Gly Met Phe Asp		
515	520	525
Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu		
530	535	540
Leu Thr Pro Ala Glu Thr Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr		
545	550	555
Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Ser Val		
565	570	575
Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr Lys		
580	585	590
Gln Ala Gly Asp Asn Phe Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val		
595	600	605
Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp Lys		
610	615	620
Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu Leu		
625	630	635
		640

SUBSTITUTE SHEET (rule 26)

Tyr Arg Leu Gly Ala Val Gln Asn Glu Val Thr Leu Thr His Pro Ile
645 650 655
Thr Lys Tyr Ile Met Ala Cys Met Ser Ala Asp Leu Glu Val Val
660 665 670

(2) INFORMATION FOR SEQ ID NO:21:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Gly Ser Gly Ser
1

(2) INFORMATION FOR SEQ ID NO:22:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Pro Ala Gly Gly
1

(2) INFORMATION FOR SEQ ID NO:22:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1964 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
(B) LOCATION: 1..1964

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 632 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

```

Met Ala Pro Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu Leu Gly
1           5           10           15

Cys Ile Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val Glu Gly
          20           25           30

Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala Thr Cys
          35           40           45

Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser Lys Thr
          50           55           60

Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn Val Asp
65           70           75           80

Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser Leu Thr
          85           90           95

Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His Ala
          100          105          110

Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser Leu Leu
          115          120          125

Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly Pro Leu
          130          135          140

Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala Val Cys
145          150          155          160

Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu Ser Met
          165          170          175

Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser Pro Pro
          180          185          190

Ala Val Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro Thr Gly
          195          200          205

Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln Gly Tyr
          210          215          220

Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly Phe Gly
225          230          235          240

```

SUBSTITUTE SHEET (rule 26)

Ala Tyr Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg Thr Gly
 245 250 255
 Val Arg Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr Tyr Gly
 260 265 270
 Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp Ile Ile
 275 280 285
 Ile Cys Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu Gly Ile
 290 295 300
 Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val
 305 310 315 320
 Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His Pro Asn
 325 330 335
 Ile Glu Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe Tyr Gly
 340 345 350
 Lys Ala Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu Ile Phe
 355 360 365
 Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu Ser Gly
 370 375 380
 Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser Val
 385 390 395 400
 Ile Pro Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala Leu Met
 405 410 415
 Thr Gly Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys
 420 425 430
 Val Thr Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile Glu
 435 440 445
 Thr Thr Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg Arg Gly
 450 455 460
 Arg Thr Gly Arg Gly Arg Arg Gly Ile Tyr Arg Phe Val Thr Pro Gly
 465 470 475 480
 Glu Arg Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu Cys Tyr
 485 490 495
 Asp Ala Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr Ser Val
 500 505 510
 Arg Leu Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys Gln Asp
 515 520 525
 His Leu Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His Ile Asp
 530 535 540

Ala His Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe Pro Tyr
 545 550 555 560

Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro
 565 570 575

Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr
 580 585 590

Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn
 595 600 605

Glu Val Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala Cys Met
 610 615 620

Ser Ala Asp Leu Glu Val Val Thr
 625 630

(2) INFORMATION FOR SEQ ID NO:24:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 54 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Ser Thr Trp Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr
 1 5 10 15

Cys Leu Thr Thr Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu Ser
 20 25 30

Gly Arg Pro Ala Ile Val Pro Asp Arg Glu Leu Leu Tyr Gln Glu Phe
 35 40 45

Asp Glu Met Glu Glu Cys
 50

(2) INFORMATION FOR SEQ ID NO:25:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 16 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Asp	Thr	Glu	Asp	Val	Val	Cys	Cys	Ser	Met	Tyr	Thr	Trp	Thr	Gly	Lys
1				5					10					15	

(2) INFORMATION FOR SEQ ID NO:26:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 78 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

GATATACATA TGGGTTCTGT TGTTATTGTT GGTAGAATTA TTTTATCTGG TAGTGGTAGT	60
ATCACGGCCT ACTCCCAA	78

(2) INFORMATION FOR SEQ ID NO:27:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 36 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

CTCAGCGAAT TCTCAAGACC GCATAGTAGT TTCCAT	36
---	----

(2) INFORMATION FOR SEQ ID NO:28:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 39 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

CGGGGCCTAC TTGGTTGCAA GATCACTAGC CTTACAGGC

39

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GCCTGTAAGG CTAGTGATCT TGCAACCAAG TAGGCCCCG

39

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

CGGGGCCTAC TTGGTTGCAT CAAGACTAGC CTTACAGGC

39

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

GCCTGTAAGG CTAGTCTTGA TGCAACCAAG TAGGCCCCG

39

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 base pairs
- (B) TYPE: nucleic acid

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

CGGGGCCTAC TTGGTTGCAA GAAGACTAGC CTTACAGGC

39

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

GCCTGTAAGG CTAGTCTTCT TGCAACCAAG TAGGCCCCG

39

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 40 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

CTCCTACTTG AAGGGCTCTG CTGGTGGTCC ACTGCTCTGC

40

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 40 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

GCAGAGCAGT GGACCACCAG CAGAGCCCTT CAAGTAGGAG

40

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 39 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

CGGGGCCTAC TTGGTTGCAA GATCACTAGC CTTACAGGC

39

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 39 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

GCCTGTAAGG CTAGTGATCT TGCAACCAAG TAGGCCCCG

39

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 39 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

CGGGGCCTAC TTGGTTGCAT CAAGACTAGC CTTACAGGC

39

(2) INFORMATION FOR SEQ ID NO:39:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

GCCTGTAAGG CTAGTCTTGA TGCAACCAAG TAGGCCCCG

39

(2) INFORMATION FOR SEQ ID NO:40:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

CGGGGCCTAC TTGGTTGCAA GAAGACTAGC CTTACAGGC

39

(2) INFORMATION FOR SEQ ID NO:41:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

GCCTGTAAGG CTAGTCTTGA TGCAACCAAG TAGGCCCCG

39

(2) INFORMATION FOR SEQ ID NO:42:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 78 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

GATATACATA TGGGTTCTGT TGTTATTGTT GGTAGAATTA TTTTATCTCC TGCTGGTGGT 60
ATCACGGCCT ACTCCCAA 78

(2) INFORMATION FOR SEQ ID NO:43:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

CTCAGCGAAT TCTCAAGACC GCATAGTAGT TTCCAT 36

(2) INFORMATION FOR SEQ ID NO:44:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

CGGGGCCTAC TTGGTTGCAA GATCACTAGC CTTACAGGC 39

(2) INFORMATION FOR SEQ ID NO:45:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

GCCTGTAAGG CTAGTGATCT TGCAACCAAG TAGGCCCCG

39

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 216 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

```

Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro
 1               5               10               15

Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu
      20               25               30

Ser Pro Ala Gly Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu Leu
      35               40               45

Gly Cys Ile Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val Glu
      50               55               60

Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala Thr
      65               70               75               80

Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser Lys
      85               90               95

Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn Val
      100              105              110

Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser Leu
      115              120              125

Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His
      130              135              140

Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser Leu
      145              150              155              160

Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly Pro
      165              170              175

Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala Val
      180              185              190

Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu Ser
      195              200              205

Met Glu Thr Thr Met Arg Ser *
      210              215

```

SUBSTITUTE SHEET (rule 26)

(2) INFORMATION FOR SEQ ID NO:47:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 3 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

Pro Ala Gly
1

(2) INFORMATION FOR SEQ ID NO:48:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 75 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

GATATACATA TGGGTTCTGT TGTTATTGTT GGTAGAATTA TTTTATCTCC TGCTGGTATC 60
ACGGCCTACT CCCAA 75

(2) INFORMATION FOR SEQ ID NO:49:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 36 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

CTCAGCGAAT TCTCAAGACC GCATAGTAGT TTCCAT 36

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 213 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

```

Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro
 1              5              10              15

Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu
      20              25              30

Ser Pro Ala Gly Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu Leu
      35              40              45

Gly Cys Lys Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val Glu
 50              55              60

Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala Thr
 65              70              75              80

Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser Lys
      85              90              95

Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn Val
      100              105              110

Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser Leu
      115              120              125

Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His
      130              135              140

Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser Leu
      145              150              155              160

Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly Pro
      165              170              175

Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala Val
      180              185              190

Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu Ser
      195              200              205

Met Glu Thr Thr Met
      210

```

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

CGGGGCCTAC TTGGTTGCAA GATCACTAGC CTTACAGGC

39

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

GCCTGTAAGG CTAGTGATCT TGCAACCAAG TAGGCCCCG

39

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 166 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Met	Ile	Thr	Ser	Leu	Thr	Gly	Arg	Asp	Lys	Asn	Gln	Val	Glu	Gly	Glu	
1				5					10					15		
Val	Gln	Val	Val	Ser	Thr	Ala	Thr	Gln	Ser	Phe	Leu	Ala	Thr	Cys	Val	
			20					25					30			
Asn	Gly	Val	Cys	Trp	Thr	Val	Tyr	His	Gly	Ala	Gly	Ser	Lys	Thr	Leu	
		35					40					45				
Ala	Gly	Pro	Lys	Gly	Pro	Ile	Thr	Gln	Met	Tyr	Thr	Asn	Val	Asp	Gln	
		50				55					60					
Asp	Leu	Val	Gly	Trp	Gln	Ala	Pro	Pro	Gly	Ala	Arg	Ser	Leu	Thr	Pro	
65					70				75						80	
Cys	Thr	Cys	Gly	Ser	Ser	Asp	Leu	Tyr	Leu	Val	Thr	Arg	His	Ala	Asp	
				85					90						95	

Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser Leu Leu Ser
 100 105 110

Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly Pro Leu Leu
 115 120 125

Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala Val Cys Thr
 130 135 140

Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu Ser Met Glu
 145 150 155 160

Thr Thr Met Arg Ser *
 165

(2) INFORMATION FOR SEQ ID NO:54:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 3 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Gly Gly Ser
 1

(2) INFORMATION FOR SEQ ID NO:55:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 75 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

GATATACATA TGGGTTCTGT TGTTATTGTT GGTAGAATTA TTTTATCTGG TGGTTCTATC 60

ACGGCCTACT CCAA 75

(2) INFORMATION FOR SEQ ID NO:56:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 36 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

CTCAGCGAAT TCTCAAGACC GCATAGTAGT TTCCAT

36

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 216 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

```

Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro
 1             5             10             15

Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu
      20             25             30

Ser Gly Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu Leu
      35             40             45

Gly Cys Lys Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val Glu
      50             55             60

Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala Thr
      65             70             75             80

Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser Lys
      85             90             95

Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn Val
      100            105            110

Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser Leu
      115            120            125

Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His
      130            135            140

Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser Leu
      145            150            155            160

Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly Pro
      165            170            175

Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala Val

```

SUBSTITUTE SHEET (rule 26)

180 185 190
Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu Ser
195 200 205
Met Glu Thr Thr Met Arg Ser *
210 215

(2) INFORMATION FOR SEQ ID NO:58:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

CGGGGCCTAC TTGGTTGCAA GATCACTAGC CTTACAGGC 39

(2) INFORMATION FOR SEQ ID NO:59:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

GCCTGTAAGG CTAGTGATCT TGCAACCAAG TAGGCCCCG 39

(2) INFORMATION FOR SEQ ID NO:60:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 668 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Met His Met His His His His His His Leu Val Pro Arg Gly Ser Ala
1 5 10 15
Pro Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu Leu Gly Cys Lys
20 25 30

Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val Glu Gly Glu Val
 35 40 45
 Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala Thr Cys Val Asn
 50 55 60
 Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser Lys Thr Leu Ala
 65 70 75 80
 Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn Val Asp Gln Asp
 85 90 95
 Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser Leu Thr Pro Cys
 100 105 110
 Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His Ala Asp Val
 115 120 125
 Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro
 130 135 140
 Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly Pro Leu Leu Cys
 145 150 155 160
 Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala Val Cys Thr Arg
 165 170 175
 Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu Ser Met Glu Thr
 180 185 190
 Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser Pro Pro Ala Val
 195 200 205
 Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro Thr Gly Ser Gly
 210 215 220
 Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val
 225 230 235 240
 Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr
 245 250 255
 Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg
 260 265 270
 Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr Tyr Gly Lys Phe
 275 280 285
 Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys
 290 295 300
 Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu Gly Ile Gly Thr
 305 310 315 320
 Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala
 325 330 335
 Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His Pro Asn Ile Glu

340	345	350
Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala 355	360	365
Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu Ile Phe Cys His 370	375	380
Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu Ser Gly Leu Gly 385	390	395 400
Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro 405	410	415
Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala Leu Met Thr Gly 420	425	430
Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr 435	440	445
Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr 450	455	460
Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg Arg Gly Arg Thr 465	470	475 480
Gly Arg Gly Arg Arg Gly Ile Tyr Arg Phe Val Thr Pro Gly Glu Arg 485	490	495
Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala 500	505	510
Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr Ser Val Arg Leu 515	520	525
Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu 530	535	540
Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His Ile Asp Ala His 545	550	555 560
Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe Pro Tyr Leu Val 565	570	575
Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser 580	585	590
Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His 595	600	605
Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Val 610	615	620
Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala Cys Met Ser Ala 625	630	635 640
Asp Leu Glu Val Val Thr * Glu Phe Glu Leu Arg Arg Gln Ala Cys 645	650	655

SUBSTITUTE SHEET (rule 26)

Gly Arg Thr Arg Ala Pro Pro Pro Pro Pro Leu Arg
660 665

(2) INFORMATION FOR SEQ ID NO:61:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 39 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

CGGGGCCTAC TTGGTTGCAA GATCACTAGC CTTACAGGC

39

(2) INFORMATION FOR SEQ ID NO:62:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 39 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

GCCTGTAAGG CTAGTGATCT TGCAACCAAG TAGGCCCCG

39

(2) INFORMATION FOR SEQ ID NO:63:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 668 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

Met His Met His His His His His His Leu Val Pro Arg Gly Ser Ala
1 5 10 15

Pro Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu Leu Gly Cys Ile
20 25 30

Lys Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val Glu Gly Glu Val

SUBSTITUTE SHEET (rule 26)

35	40	45
Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala Thr Cys Val Asn		
50	55	60
Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser Lys Thr Leu Ala		
65	70	75
Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn Val Asp Gln Asp		
	85	90
Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser Leu Thr Pro Cys		
	100	105
Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His Ala Asp Val		
	115	120
Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro		
	130	135
Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly Pro Leu Leu Cys		
	145	150
Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala Val Cys Thr Arg		
	165	170
Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu Ser Met Glu Thr		
	180	185
Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser Pro Pro Ala Val		
	195	200
Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro Thr Gly Ser Gly		
	210	215
Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val		
	225	230
Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr		
	245	250
Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg		
	260	265
Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr Tyr Gly Lys Phe		
	275	280
Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys		
	290	295
Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu Gly Ile Gly Thr		
	305	310
Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala		
	325	330
Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His Pro Asn Ile Glu		
	340	345
		350

SUBSTITUTE SHEET (rule 26)

Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala
 355 360 365
 Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu Ile Phe Cys His
 370 375 380
 Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu Ser Gly Leu Gly
 385 390 395 400
 Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro
 405 410 415
 Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala Leu Met Thr Gly
 420 425 430
 Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr
 435 440 445
 Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr
 450 455 460
 Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg Arg Gly Arg Thr
 465 470 475 480
 Gly Arg Gly Arg Arg Gly Ile Tyr Arg Phe Val Thr Pro Gly Glu Arg
 485 490 495
 Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala
 500 505 510
 Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr Ser Val Arg Leu
 515 520 525
 Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu
 530 535 540
 Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His Ile Asp Ala His
 545 550 555 560
 Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe Pro Tyr Leu Val
 565 570 575
 Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser
 580 585 590
 Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His
 595 600 605
 Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Val
 610 615 620
 Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala Cys Met Ser Ala
 625 630 635 640
 Asp Leu Glu Val Val Thr *

(2) INFORMATION FOR SEQ ID NO:64:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 39 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

CGGGGCCTAC TTGGTTGCAT CAAGACTAGC CTTACAGGC

39

(2) INFORMATION FOR SEQ ID NO:65:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 39 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

GCCTGTAAGG CTAGTCTTGA TGCAACCAAG TAGGCCCCG

39

(2) INFORMATION FOR SEQ ID NO:66:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 668 amino acids
 - (B) TYPE: amino acid
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

Met	His	Met	His	His	His	His	His	His	Leu	Val	Pro	Arg	Gly	Ser	Ala
1				5					10					15	
Pro	Ile	Thr	Ala	Tyr	Ser	Gln	Gln	Thr	Arg	Gly	Leu	Leu	Gly	Cys	Ile
			20					25					30		
Ile	Thr	Ser	Leu	Thr	Gly	Arg	Asp	Lys	Asn	Gln	Val	Glu	Gly	Glu	Val
			35				40						45		
Gln	Val	Val	Ser	Thr	Ala	Thr	Gln	Ser	Phe	Leu	Ala	Thr	Cys	Val	Asn
		50					55						60		

Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser Lys Thr Leu Ala
 65 70 75 80

Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn Val Asp Gln Asp
 85 90 95

Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser Leu Thr Pro Cys
 100 105 110

Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His Ala Asp Val
 115 120 125

Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro
 130 135 140

Arg Pro Val Ser Tyr Leu Lys Gly Ser Ala Gly Gly Pro Leu Leu Cys
 145 150 155 160

Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala Val Cys Thr Arg
 165 170 175

Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu Ser Met Glu Thr
 180 185 190

Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser Pro Pro Ala Val
 195 200 205

Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro Thr Gly Ser Gly
 210 215 220

Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val
 225 230 235 240

Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr
 245 250 255

Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg
 260 265 270

Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr Tyr Gly Lys Phe
 275 280 285

Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys
 290 295 300

Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu Gly Ile Gly Thr
 305 310 315 320

Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala
 325 330 335

Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His Pro Asn Ile Glu
 340 345 350

Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala
 355 360 365

SUBSTITUTE SHEET (rule 26)

Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu Ile Phe Cys His
 370 375 380
 Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu Ser Gly Leu Gly
 385 390 395 400
 Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro
 405 410 415
 Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala Leu Met Thr Gly
 420 425 430
 Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr
 435 440 445
 Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr
 450 455 460
 Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg Arg Gly Arg Thr
 465 470 475 480
 Gly Arg Gly Arg Arg Gly Ile Tyr Arg Phe Val Thr Pro Gly Glu Arg
 485 490 495
 Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala
 500 505 510
 Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr Ser Val Arg Leu
 515 520 525
 Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu
 530 535 540
 Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His Ile Asp Ala His
 545 550 555 560
 Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe Pro Tyr Leu Val
 565 570 575
 Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser
 580 585 590
 Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His
 595 600 605
 Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Val
 610 615 620
 Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala Cys Met Ser Ala
 625 630 635 640
 Asp Leu Glu Val Val Thr *

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 40 base pairs

SUBSTITUTE SHEET (rule 26)

- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

CTCCTACTTG AAGGGCTCTG CTGGTGGTCC ACTGCTCTGC

40

(2) INFORMATION FOR SEQ ID NO:68:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 40 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

GCAGAGCAGT GGACCACCAG CAGAGCCCTT CAAGTAGGAG

40

(2) INFORMATION FOR SEQ ID NO:69:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 668 amino acids
 - (B) TYPE: amino acid
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

Met	His	Met	His	His	His	His	His	His	Leu	Val	Pro	Arg	Gly	Ser	Ala
1				5					10					15	
Pro	Ile	Thr	Ala	Tyr	Ser	Gln	Gln	Thr	Arg	Gly	Leu	Leu	Gly	Cys	Ile
			20					25					30		
Ile	Thr	Ser	Leu	Thr	Gly	Arg	Asp	Lys	Asn	Gln	Val	Glu	Gly	Glu	Val
		35					40						45		
Gln	Val	Val	Ser	Thr	Ala	Thr	Gln	Ser	Phe	Leu	Ala	Thr	Cys	Val	Asn
	50					55					60				
Gly	Val	Cys	Trp	Thr	Val	Tyr	His	Gly	Ala	Gly	Ser	Lys	Thr	Leu	Ala
65					70					75					80

↓SDOCID: <WO_8928482A2 | >

385	390	395	400
Ile Asn Ala Val	Ala Tyr Tyr Arg Gly	Leu Asp Val Ser Val	Ile Pro
	405	410	415
Thr Ser Gly Asp	Val Val Val Val	Ala Thr Asp Ala	Leu Met Thr Gly
	420	425	430
Tyr Thr Gly Asp	Phe Asp Ser Val	Ile Asp Cys Asn	Thr Cys Val Thr
	435	440	445
Gln Thr Val Asp	Phe Ser Leu Asp	Pro Thr Phe Thr	Ile Glu Thr Thr
	450	455	460
Thr Val Pro Gln	Asp Ala Val Ser	Arg Ser Gln Arg	Arg Gly Arg Thr
	465	470	475
Gly Arg Gly Arg	Arg Gly Ile Tyr	Arg Phe Val Thr	Pro Gly Glu Arg
	485	490	495
Pro Ser Gly Met	Phe Asp Ser Ser	Val Leu Cys Glu	Cys Tyr Asp Ala
	500	505	510
Gly Cys Ala Trp	Tyr Glu Leu Thr	Pro Ala Glu Thr	Ser Val Arg Leu
	515	520	525
Arg Ala Tyr Leu	Asn Thr Pro Gly	Leu Pro Val Cys	Gln Asp His Leu
	530	535	540
Glu Phe Trp Glu	Ser Val Phe Thr	Gly Leu Thr His	Ile Asp Ala His
	545	550	555
Phe Leu Ser Gln	Thr Lys Gln Ala	Gly Asp Asn Phe	Pro Tyr Leu Val
	565	570	575
Ala Tyr Gln Ala	Thr Val Cys Ala	Arg Ala Gln Ala	Pro Pro Pro Ser
	580	585	590
Trp Asp Gln Met	Trp Lys Cys Leu	Ile Arg Leu Lys	Pro Thr Leu His
	595	600	605
Gly Pro Thr Pro	Leu Leu Tyr Arg	Leu Gly Ala Val	Gln Asn Glu Val
	610	615	620
Thr Leu Thr His	Pro Ile Thr Lys	Tyr Ile Met Ala	Cys Met Ser Ala
	625	630	635
Asp Leu Glu Val	Val Thr *	Glu Phe Glu Leu	Arg Arg Gln Ala Cys
	645	650	655
Gly Arg Thr Arg	Ala Pro Pro Pro	Pro Pro Leu Arg	
	660	665	

(2) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 35 base pairs

(B) TYPE: nucleic acid

SUBSTITUTE SHEET (rule 26)

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

GTCCGTCATA CCAACTTCCG GAGACGTCGT TGTCG

35

(2) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

CGACAACGAC GTCTCCGAA GTTGGTATGA CGGAC

35

(2) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 669 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

Met	His	Met	His	His	His	His	His	His	Leu	Val	Pro	Arg	Gly	Ser	Ala
1				5					10					15	
Pro	Ile	Thr	Ala	Tyr	Ser	Gln	Gln	Thr	Arg	Gly	Leu	Leu	Gly	Cys	Ile
			20					25					30		
Ile	Thr	Ser	Leu	Thr	Gly	Arg	Asp	Lys	Asn	Gln	Val	Glu	Gly	Glu	Val
			35				40					45			
Gln	Val	Val	Ser	Thr	Ala	Thr	Gln	Ser	Phe	Leu	Ala	Thr	Cys	Val	Asn
			50				55					60			
Gly	Val	Cys	Trp	Thr	Val	Tyr	His	Gly	Ala	Gly	Ser	Lys	Thr	Leu	Ala
			65				70				75			80	
Gly	Pro	Lys	Gly	Pro	Ile	Thr	Gln	Met	Tyr	Thr	Asn	Val	Asp	Gln	Asp

85										90					95				
Leu	Val	Gly	Trp	Gln	Ala	Pro	Pro	Gly	Ala	Arg	Ser	Leu	Thr	Pro	Cys				
			100						105				110						
Thr	Cys	Gly	Ser	Ser	Asp	Leu	Tyr	Leu	Val	Thr	Arg	His	Ala	Asp	Val				
		115					120					125							
Ile	Pro	Val	Arg	Arg	Arg	Gly	Asp	Ser	Arg	Gly	Ser	Leu	Leu	Ser	Pro				
	130					135					140								
Arg	Pro	Val	Ser	Tyr	Leu	Lys	Gly	Ser	Ser	Gly	Gly	Pro	Leu	Leu	Cys				
145					150					155					160				
Pro	Ser	Gly	His	Ala	Val	Gly	Ile	Phe	Arg	Ala	Ala	Val	Cys	Thr	Arg				
			165						170					175					
Gly	Val	Ala	Lys	Ala	Val	Asp	Phe	Val	Pro	Val	Glu	Ser	Met	Glu	Thr				
		180						185					190						
Thr	Met	Arg	Ser	Pro	Val	Phe	Thr	Asp	Asn	Ser	Ser	Pro	Pro	Ala	Val				
	195						200					205							
Pro	Gln	Ser	Phe	Gln	Val	Ala	His	Leu	His	Ala	Pro	Thr	Gly	Ser	Gly				
	210					215					220								
Lys	Ser	Thr	Lys	Val	Pro	Ala	Ala	Tyr	Ala	Ala	Gln	Gly	Tyr	Lys	Val				
225					230					235					240				
Leu	Val	Leu	Asn	Pro	Ser	Val	Ala	Ala	Thr	Leu	Gly	Phe	Gly	Ala	Tyr				
			245						250					255					
Met	Ser	Lys	Ala	His	Gly	Ile	Asp	Pro	Asn	Ile	Arg	Thr	Gly	Val	Arg				
		260						265					270						
Thr	Ile	Thr	Thr	Gly	Ala	Pro	Val	Thr	Tyr	Ser	Thr	Tyr	Gly	Lys	Phe				
	275						280					285							
Leu	Ala	Asp	Gly	Gly	Cys	Ser	Gly	Gly	Ala	Tyr	Asp	Ile	Ile	Ile	Cys				
	290					295					300								
Asp	Glu	Cys	His	Ser	Thr	Asp	Ser	Thr	Thr	Ile	Leu	Gly	Ile	Gly	Thr				
305					310					315				320					
Val	Leu	Asp	Gln	Ala	Glu	Thr	Ala	Gly	Ala	Arg	Leu	Val	Val	Leu	Ala				
			325						330					335					
Thr	Ala	Thr	Pro	Pro	Gly	Ser	Val	Thr	Val	Pro	His	Pro	Asn	Ile	Glu				
		340						345					350						
Glu	Val	Ala	Leu	Ser	Asn	Thr	Gly	Glu	Ile	Pro	Phe	Tyr	Gly	Lys	Ala				
	355						360					365							
Ile	Pro	Ile	Glu	Ala	Ile	Arg	Gly	Gly	Arg	His	Leu	Ile	Phe	Cys	His				
	370					375					380								
Ser	Lys	Lys	Lys	Cys	Asp	Glu	Leu	Ala	Ala	Lys	Leu	Ser	Gly	Leu	Gly				
385					390					395					400				

SUBSTITUTE SHEET (rule 26)

```

Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro
      405                      410                      415

Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala Leu Met Thr Gly
      420                      425                      430

Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr
      435                      440                      445

Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr
      450                      455                      460

Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg Arg Gly Arg Thr
      465                      470                      475                      480

Gly Arg Gly Arg Arg Gly Ile Tyr Arg Phe Val Thr Pro Gly Glu Arg
      485                      490                      495

Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala
      500                      505                      510

Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr Ser Val Arg Leu
      515                      520                      525

Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu
      530                      535                      540

Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His Ile Asp Ala His
      545                      550                      555                      560

Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe Pro Tyr Leu Val
      565                      570                      575

Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser
      580                      585                      590

Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His
      595                      600                      605

Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Val
      610                      615                      620

Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala Cys Met Ser Ala
      625                      630                      635                      640

Asp Leu Glu Val Val Thr *
```

(2) INFORMATION FOR SEQ ID NO:73:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 33 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

SUBSTITUTE SHEET (rule 26)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

ACTAAAGTGC CGGCTGCCTA CGCAGCCCAA GGG

33

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 33 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

CCCTTGGGCT GCGTAGGCAG CCGGCACTTT AGT

33

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

CGGGGCCTAC TTGGTTGCAA GATCACTAGC CTTACAGGC

39

(2) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

GCCTGTAAGG CTAGTGATCT TGCAACCAAG TAGGCCCCG

39

SUBSTITUTE SHEET (rule 26)

(2) INFORMATION FOR SEQ ID NO:77:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

CGGGGCCTAC TTGGTTGCAT CAAGACTAGC CTTACAGGC

39

(2) INFORMATION FOR SEQ ID NO:78:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

GCCTGTAAGG CTAGTCTTGA TGCAACCAAG TAGGCCCCG

39

(2) INFORMATION FOR SEQ ID NO:79:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

CGGGGCCTAC TTGGTTGCAA GAAGACTAGC CTTACAGG

38

(2) INFORMATION FOR SEQ ID NO:80:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

GCCTGTAAGG CTAGTCTTCT TGCAACCAAG TAGGCCCCG

39

(2) INFORMATION FOR SEQ ID NO:81:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 39 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

CGGGGCCTAC TTGGTTGCAA GATCACTAGC CTTACAGGC

39

(2) INFORMATION FOR SEQ ID NO:82:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 39 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

GCCTGTAAGG CTAGTGATCT TGCAACCAAG TAGGCCCCG

39

(2) INFORMATION FOR SEQ ID NO:83:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 39 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

CGGGGCCTAC TTGGTTGCAT CAAGACTAGC CTTACAGGC

39

(2) INFORMATION FOR SEQ ID NO:84:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

GCCTGTAAGG CTAGTCTTGA TGCAACCAAG TAGGCCCCCG

39

(2) INFORMATION FOR SEQ ID NO:85:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

CGGGGCCTAC TTGGTTGCAA GAAGACTAGC CTTACAGGC

39

(2) INFORMATION FOR SEQ ID NO:86:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

GCCTGTAAGG CTAGTCTTCT TGCAACCAAG TAGGCCCCCG

39

(2) INFORMATION FOR SEQ ID NO:87:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 96 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

GATATACATA TGGCTTACTC TCTGACTACG GGTTCGTGTTG TTATTGTTGG TAGAATTATT 60
TTATCTGGTA GTGGTAGTAT CACGGCCTAC TCCCAA 96

(2) INFORMATION FOR SEQ ID NO:88:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 51 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

GTGGTGGTGC TCGAGGCTGC CGCGCGGCAC CAGCGTAACG ACCTCCAGGT C 51

(2) INFORMATION FOR SEQ ID NO:89:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 96 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

GATATACATA TGGCTTACTC TCTGACTACG GGTTCGTGTTG TTATTGTTGG TAGAATTATT 60
TTATCTGGTA GTGGTAGTAT CACGGCCTAC TCCCAA 96

(2) INFORMATION FOR SEQ ID NO:90:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 50 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

TGGTGGTGCT CGAGGCTGCC GCGCGGCACC AGCGTAACGA CCTCCAGGTC

50

(2) INFORMATION FOR SEQ ID NO:91:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

Asp	Thr	Glu	Asp	Val	Val	Ala	Cys	Ser	Met	Ser	Tyr	Thr	Trp	Tyr	Gly
1				5					10					15	

Lys

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 651 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..651

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

ATG	GGC	AGC	AGC	CAT	CAT	CAT	CAT	CAT	CAC	AGC	AGC	GGC	CTG	GTG	CCG	48
Met	Gly	Ser	Ser	His	His	His	His	His	His	Ser	Ser	Gly	Leu	Val	Pro	
1				5					10					15		

CGC	GGC	AGC	CAT	ATG	GGT	TCT	GTT	GTT	ATT	GTT	GGT	AGA	ATT	ATT	TTA	96
Arg	Gly	Ser	His	Met	Gly	Ser	Val	Val	Ile	Val	Gly	Arg	Ile	Ile	Leu	
			20					25					30			

SUBSTITUTE SHEET (rule 26)

TCT	GGT	AGT	GGT	AGT	ATC	ACG	GCC	TAC	TCC	CAA	CAG	ACG	CGG	GGC	CTA	144
Ser	Gly	Ser	Gly	Ser	Ile	Thr	Ala	Tyr	Ser	Gln	Gln	Thr	Arg	Gly	Leu	
		35					40					45				
CTT	GGT	TGC	ATC	ATC	ACT	AGC	CTT	ACA	GGC	CGG	GAC	AAG	AAC	CAG	GTC	192
Leu	Gly	Cys	Ile	Ile	Thr	Ser	Leu	Thr	Gly	Arg	Asp	Lys	Asn	Gln	Val	
		50				55					60					
GAG	GGA	GAG	GTT	CAG	GTG	GTT	TCC	ACC	GCA	ACA	CAA	TCC	TTC	CTG	GCG	240
Glu	Gly	Glu	Val	Gln	Val	Val	Ser	Thr	Ala	Thr	Gln	Ser	Phe	Leu	Ala	
		65				70					75				80	
ACC	TGC	GTC	AAC	GGC	GTG	TGT	TGG	ACC	GTT	TAC	CAT	GGT	GCT	GGC	TCA	288
Thr	Cys	Val	Asn	Gly	Val	Cys	Trp	Thr	Val	Tyr	His	Gly	Ala	Gly	Ser	
				85						90				95		
AAG	ACC	TTA	GCC	GGC	CCA	AAG	GGG	CCA	ATC	ACC	CAG	ATG	TAC	ACT	AAT	336
Lys	Thr	Leu	Ala	Gly	Pro	Lys	Gly	Pro	Ile	Thr	Gln	Met	Tyr	Thr	Asn	
			100					105					110			
GTG	GAC	CAG	GAC	CTC	GTC	GGC	TGG	CAG	GCG	CCC	CCC	GGG	GCG	CGT	TCC	384
Val	Asp	Gln	Asp	Leu	Val	Gly	Trp	Gln	Ala	Pro	Pro	Gly	Ala	Arg	Ser	
		115					120					125				
TTG	ACA	CCA	TGC	ACC	TGT	GGC	AGC	TCA	GAC	CTT	TAC	TTG	GTC	ACG	AGA	432
Leu	Thr	Pro	Cys	Thr	Cys	Gly	Ser	Ser	Asp	Leu	Tyr	Leu	Val	Thr	Arg	
		130				135					140					
CAT	GCT	GAC	GTC	ATT	CCG	GTG	CGC	CGG	CGG	GGC	GAC	AGT	AGG	GGG	AGC	480
His	Ala	Asp	Val	Ile	Pro	Val	Arg	Arg	Arg	Gly	Asp	Ser	Arg	Gly	Ser	
		145				150				155					160	
CTG	CTC	TCC	CCC	AGG	CCT	GTC	TCC	TAC	TTG	AAG	GGC	TCT	TCG	GGT	GGT	528
Leu	Leu	Ser	Pro	Arg	Pro	Val	Ser	Tyr	Leu	Lys	Gly	Ser	Ser	Gly	Gly	
				165						170				175		
CCA	CTG	CTC	TGC	CCT	TCG	GGG	CAC	GCT	GTG	GGC	ATC	TTC	CGG	GCT	GCC	576
Pro	Leu	Leu	Cys	Pro	Ser	Gly	His	Ala	Val	Gly	Ile	Phe	Arg	Ala	Ala	
			180							185				190		
GTA	TGC	ACC	CGG	GGG	GTT	GCG	AAG	GCG	GTG	GAC	TTT	GTG	CCC	GTA	GAG	624
Val	Cys	Thr	Arg	Gly	Val	Ala	Lys	Ala	Val	Asp	Phe	Val	Pro	Val	Glu	
		195					200					205				
TCC	ATG	GAA	ACT	ACT	ATG	CGG	TCT	TGA								651
Ser	Met	Glu	Thr	Thr	Met	Arg	Ser	*								
		210				215										

(2) INFORMATION FOR SEQ ID NO:93:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 651 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..651

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

ATG GGC AGC AGC CAT CAT CAT CAT CAT CAC AGC AGC GGC CTG GTG CCG	48
Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro	
1 5 10 15	
CGC GGC AGC CAT ATG GGT TCT GTT GTT ATT GTT GGT AGA ATT ATT TTA	96
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu	
20 25 30	
TCT GGT AGT GGT AGT ATC ACG GCC TAC TCC CAA CAG ACG CGG GGC CTA	144
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu	
35 40 45	
CTT GGT TGC AAG ATC ACT AGC CTT ACA GGC CGG GAC AAG AAC CAG GTC	192
Leu Gly Cys Lys Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val	
50 55 60	
GAG GGA GAG GTT CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG	240
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala	
65 70 75 80	
ACC TGC GTC AAC GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA	288
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser	
85 90 95	
AAG ACC TTA GCC GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT	336
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn	
100 105 110	
GTG GAC CAG GAC CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC	384
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser	
115 120 125	
TTG ACA CCA TGC ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA	432
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg	
130 135 140	
CAT GCT GAC GTC ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC	480
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser	
145 150 155 160	
CTG CTC TCC CCC AGG CCT GTC TCC TAC TTG AAG GGC TCT TCG GGT GGT	528
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly	
165 170 175	
CCA CTG CTC TGC CCT TCG GGG CAC GCT GTG GGC ATC TTC CGG GCT GCC	576
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala	
180 185 190	
GTA TGC ACC CGG GGG GTT GCG AAG GCG GTG GAC TTT GTG CCC GTA GAG	624

Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu
 195 200 205

TCC ATG GAA ACT ACT ATG CGG TCT TGA 651
 Ser Met Glu Thr Thr Met Arg Ser *
 210 215

(2) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 651 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..651

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

ATG GGC AGC AGC CAT CAT CAT CAT CAC AGC AGC GGC CTG GTG CCG	48
Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro	
1 5 10 15	
CGC GGC AGC CAT ATG GGT TCT GTT GTT ATT GTT GGT AGA ATT ATT TTA	96
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu	
20 25 30	
TCT GGT AGT GGT AGT ATC ACG GCC TAC TCC CAA CAG ACG CGG GGC CTA	144
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu	
35 40 45	
CTT GGT TGC ATC AAG ACT AGC CTT ACA GGC CGG GAC AAG AAC CAG GTC	192
Leu Gly Cys Ile Lys Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val	
50 55 60	
GAG GGA GAG GTT CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG	240
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala	
65 70 75 80	
ACC TGC GTC AAC GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA	288
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser	
85 90 95	
AAG ACC TTA GCC GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT	336
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn	
100 105 110	
GTG GAC CAG GAC CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC	384
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser	
115 120 125	
TTG ACA CCA TGC ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA	432

Leu	Thr	Pro	Cys	Thr	Cys	Gly	Ser	Ser	Asp	Leu	Tyr	Leu	Val	Thr	Arg		
130						135					140						
CAT	GCT	GAC	GTC	ATT	CCG	GTG	CGC	CGG	CGG	GGC	GAC	AGT	AGG	GGG	AGC	480	
His	Ala	Asp	Val	Ile	Pro	Val	Arg	Arg	Arg	Gly	Asp	Ser	Arg	Gly	Ser		
145					150					155					160		
CTG	CTC	TCC	CCC	AGG	CCT	GTC	TCC	TAC	TTG	AAG	GGC	TCT	TCG	GGT	GGT	528	
Leu	Leu	Ser	Pro	Arg	Pro	Val	Ser	Tyr	Leu	Lys	Gly	Ser	Ser	Gly	Gly		
				165					170					175			
CCA	CTG	CTC	TGC	CCT	TCG	GGG	CAC	GCT	GTG	GGC	ATC	TTC	CGG	GCT	GCC	576	
Pro	Leu	Leu	Cys	Pro	Ser	Gly	His	Ala	Val	Gly	Ile	Phe	Arg	Ala	Ala		
			180					185					190				
GTA	TGC	ACC	CGG	GGG	GTT	GCG	AAG	GCG	GTG	GAC	TTT	GTG	CCC	GTA	GAG	624	
Val	Cys	Thr	Arg	Gly	Val	Ala	Lys	Ala	Val	Asp	Phe	Val	Pro	Val	Glu		
		195					200					205					
TCC	ATG	GAA	ACT	ACT	ATG	CGG	TCT	TGA								651	
Ser	Met	Glu	Thr	Thr	Met	Arg	Ser	*									
	210					215											

(2) INFORMATION FOR SEQ ID NO:95:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 651 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..651

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

ATG	GGC	AGC	AGC	CAT	CAT	CAT	CAT	CAT	CAC	AGC	AGC	GGC	CTG	GTG	CCG	48	
Met	Gly	Ser	Ser	His	His	His	His	His	His	Ser	Ser	Gly	Leu	Val	Pro		
1				5					10					15			
CGC	GGC	AGC	CAT	ATG	GGT	TCT	GTT	GTT	ATT	GTT	GGT	AGA	ATT	ATT	TTA	96	
Arg	Gly	Ser	His	Met	Gly	Ser	Val	Val	Ile	Val	Gly	Arg	Ile	Ile	Leu		
			20					25					30				
TCT	GGT	AGT	GGT	AGT	ATC	ACG	GCC	TAC	TCC	CAA	CAG	ACG	CGG	GGC	CTA	144	
Ser	Gly	Ser	Gly	Ser	Ile	Thr	Ala	Tyr	Ser	Gln	Gln	Thr	Arg	Gly	Leu		
			35				40					45					
CTT	GGT	TGC	AAG	AAG	ACT	AGC	CTT	ACA	GGC	CGG	GAC	AAG	AAC	CAG	GTC	192	
Leu	Gly	Cys	Lys	Lys	Thr	Ser	Leu	Thr	Gly	Arg	Asp	Lys	Asn	Gln	Val		
		50					55					60					

GAG GGA GAG GTT CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG	240
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala	
65 70 75 80	
ACC TGC GTC AAC GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA	288
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser	
85 90 95	
AAG ACC TTA GCC GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT	336
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn	
100 105 110	
GTG GAC CAG GAC CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC	384
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser	
115 120 125	
TTG ACA CCA TGC ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA	432
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg	
130 135 140	
CAT GCT GAC GTC ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC	480
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser	
145 150 155 160	
CTG CTC TCC CCC AGG CCT GTC TCC TAC TTG AAG GGC TCT TCG GGT GGT	528
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly	
165 170 175	
CCA CTG CTC TGC CCT TCG GGC CAC GCT GTG GGC ATC TTC CGG GCT GCC	576
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala	
180 185 190	
GTA TGC ACC CGG GGG GTT GCG AAG GCG GTG GAC TTT GTG CCC GTA GAG	624
Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu	
195 200 205	
TCC ATG GAA ACT ACT ATG CGG TCT TGA	651
Ser Met Glu Thr Thr Met Arg Ser *	
210 215	

(2) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 650 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..650

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

ATG GGC AGC AGC CAT CAT CAT CAT CAT CAC AGC AGC GGC CTG GTG CCG	48
Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro	
1 5 10 15	
CGC GGC AGC CAT ATG GGT TCT GTT GTT ATT GTT GGT AGA ATT ATT TTA	96
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu	
20 25 30	
TCT GGT AGT GGT AGT ATC ACG GCC TAC TCC CAA CAG ACG CGG GGC CTA	144
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu	
35 40 45	
CTT GGT TGC ATC ATC ACT AGC CTT ACA GGC CGG GAC AAG AAC CAG GTC	192
Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val	
50 55 60	
GAG GGA GAG GTT CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG	240
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala	
65 70 75 80	
ACC TGC GTC AAC GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA	288
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser	
85 90 95	
AAG ACC TTA GCC GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT	336
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn	
100 105 110	
GTG GAC CAG GAC CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC	384
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser	
115 120 125	
TTG ACA CCA TGC ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA	432
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg	
130 135 140	
CAT GCT GAC GTC ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC	480
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser	
145 150 155 160	
CTG CTC TCC CCC AGG CCT GTC TCC TAC TTG AAG GGC TCT GCT GGT GGT	528
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ala Gly Gly	
165 170 175	
CCA CTG CTC TGC CCT TCG GGG CAC GCT GTG GGC ATC TTC CGG GCT GCC	576
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala	
180 185 190	
GTA TGC ACC CGG GGG GTT GCG AAG GCG GTG GAC TTT GTG CCC GTA GAG	624
Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu	
195 200 205	
TCC ATG GAA ACT ACT ATG CGG TCT TG	650
Ser Met Glu Thr Thr Met Arg Ser	
210 215	

(2) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 650 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
 (B) LOCATION: 1..650

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

ATG GGC AGC AGC CAT CAT CAT CAT CAT CAC AGC AGC GGC CTG GTG CCG	48
Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro	
1 5 10 15	
CGC GGC AGC CAT ATG GGT TCT GTT GTT ATT GTT GGT AGA ATT ATT TTA	96
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu	
20 25 30	
TCT GGT AGT GGT AGT ATC ACG GCC TAC TCC CAA CAG ACG CGG GGC CTA	144
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu	
35 40 45	
CTT GGT TGC AAG ATC ACT AGC CTT ACA GGC CGG GAC AAG AAC CAG GTC	192
Leu Gly Cys Lys Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val	
50 55 60	
GAG GGA GAG GTT CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG	240
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala	
65 70 75 80	
ACC TGC GTC AAC GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA	288
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser	
85 90 95	
AAG ACC TTA GCC GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT	336
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn	
100 105 110	
GTG GAC CAG GAC CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC	384
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser	
115 120 125	
TTG ACA CCA TGC ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA	432
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg	
130 135 140	
CAT GCT GAC GTC ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC	480
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser	
145 150 155 160	

CTG CTC TCC CCC AGG CCT GTC TCC TAC TTG AAG GGC TCT GCT GGT GGT	528
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ala Gly Gly	
165 170 175	

CCA CTG CTC TGC CCT TCG GGG CAC GCT GTG GGC ATC TTC CGG GCT GCC	576
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala	
180 185 190	

GTA TGC ACC CGG GGG GTT GCG AAG GCG GTG GAC TTT GTG CCC GTA GAG	624
Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu	
195 200 205	

TCC ATG GAA ACT ACT ATG CGG TCT TG	650
Ser Met Glu Thr Thr Met Arg Ser	
210 215	

(2) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 651 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..651

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

ATG GGC AGC AGC CAT CAT CAT CAT CAT CAC AGC AGC GGC CTG GTG CCG	48
Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro	
1 5 10 15	

CGC GGC AGC CAT ATG GGT TCT GTT GTT ATT GTT GGT AGA ATT ATT TTA	96
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu	
20 25 30	

TCT GGT AGT GGT AGT ATC ACG GCC TAC TCC CAA CAG ACG CGG GGC CTA	144
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu	
35 40 45	

CTT GGT TGC ATC AAG ACT AGC CTT ACA GGC CGG GAC AAG AAC CAG GTC	192
Leu Gly Cys Ile Lys Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val	
50 55 60	

GAG GGA GAG GTT CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG	240
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala	
65 70 75 80	

ACC TGC GTC AAC GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA	288
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser	

85					90					95						
AAG	ACC	TTA	GCC	GGC	CCA	AAG	GGG	CCA	ATC	ACC	CAG	ATG	TAC	ACT	AAT	336
Lys	Thr	Leu	Ala	Gly	Pro	Lys	Gly	Pro	Ile	Thr	Gln	Met	Tyr	Thr	Asn	
			100					105					110			
GTG	GAC	CAG	GAC	CTC	GTC	GGC	TGG	CAG	GCG	CCC	CCC	GGG	GCG	CGT	TCC	384
Val	Asp	Gln	Asp	Leu	Val	Gly	Trp	Gln	Ala	Pro	Pro	Gly	Ala	Arg	Ser	
			115				120					125				
TTG	ACA	CCA	TGC	ACC	TGT	GGC	AGC	TCA	GAC	CTT	TAC	TTG	GTC	ACG	AGA	432
Leu	Thr	Pro	Cys	Thr	Cys	Gly	Ser	Ser	Asp	Leu	Tyr	Leu	Val	Thr	Arg	
			130				135				140					
CAT	GCT	GAC	GTC	ATT	CCG	GTG	CGC	CGG	CGG	GGC	GAC	AGT	AGG	GGG	AGC	480
His	Ala	Asp	Val	Ile	Pro	Val	Arg	Arg	Arg	Gly	Asp	Ser	Arg	Gly	Ser	
					150					155					160	
CTG	CTC	TCC	CCC	AGG	CCT	GTC	TCC	TAC	TTG	AAG	GGC	TCT	GCT	GGT	GGT	528
Leu	Leu	Ser	Pro	Arg	Pro	Val	Ser	Tyr	Leu	Lys	Gly	Ser	Ala	Gly	Gly	
				165					170					175		
CCA	CTG	CTC	TGC	CCT	TCG	GGG	CAC	GCT	GTG	GGC	ATC	TTC	CGG	GCT	GCC	576
Pro	Leu	Leu	Cys	Pro	Ser	Gly	His	Ala	Val	Gly	Ile	Phe	Arg	Ala	Ala	
			180					185					190			
GTA	TGC	ACC	CGG	GGG	GTT	GCG	AAG	GCG	GTG	GAC	TTT	GTG	CCC	GTA	GAG	624
Val	Cys	Thr	Arg	Gly	Val	Ala	Lys	Ala	Val	Asp	Phe	Val	Pro	Val	Glu	
			195				200					205				
TCC	ATG	GAA	ACT	ACT	ATG	CGG	TCT	TGA								651
Ser	Met	Glu	Thr	Thr	Met	Arg	Ser	*								
			210				215									

(2) INFORMATION FOR SEQ ID NO:99:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 651 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..651

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

ATG	GGC	AGC	AGC	CAT	CAT	CAT	CAT	CAT	CAC	AGC	AGC	GGC	CTG	GTG	CCG	48
Met	Gly	Ser	Ser	His	His	His	His	His	His	Ser	Ser	Gly	Leu	Val	Pro	
1				5				10						15		

CGC GGC AGC CAT ATG GGT TCT GTT GTT ATT GTT GGT AGA ATT ATT TTA	96
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu	
20 25 30	
TCT GGT AGT GGT AGT ATC ACG GCC TAC TCC CAA CAG ACG CGG GGC CTA	144
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu	
35 40 45	
CTT GGT TGC AAG AAG ACT AGC CTT ACA GGC CGG GAC AAG AAC CAG GTC	192
Leu Gly Cys Lys Lys Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val	
50 55 60	
GAG GGA GAG GTT CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG	240
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala	
65 70 75 80	
ACC TGC GTC AAC GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA	288
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser	
85 90 95	
AAG ACC TTA GCC GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT	336
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn	
100 105 110	
GTG GAC CAG GAC CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC	384
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser	
115 120 125	
TTG ACA CCA TGC ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA	432
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg	
130 135 140	
CAT GCT GAC GTC ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC	480
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser	
145 150 155 160	
CTG CTC TCC CCC AGG CCT GTC TCC TAC TTG AAG GGC TCT GCT GGT GGT	528
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ala Gly Gly	
165 170 175	
CCA CTG CTC TGC CCT TCG GGG CAC GCT GTG GGC ATC TTC CGG GCT GCC	576
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala	
180 185 190	
GTA TGC ACC CGG GGG GTT GCG AAG GCG GTG GAC TTT GTG CCC GTA GAG	624
Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu	
195 200 205	
TCC ATG GAA ACT ACT ATG CGG TCT TGA	651
Ser Met Glu Thr Thr Met Arg Ser *	
210 215	

(2) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 651 base pairs

(B) TYPE: nucleic acid

SUBSTITUTE SHEET (rule 26)

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..651

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

ATG GGC AGC AGC CAT CAT CAT CAT CAT CAC AGC AGC GGC CTG GTG CCG	48
Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro	
1 5 10 15	
CGC GGC AGC CAT ATG GGT TCT GTT GTT ATT GTT GGT AGA ATT ATT TTA	96
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu	
20 25 30	
TCT CCT GCT GGT GGT ATC ACG GCC TAC TCC CAA CAG ACG CGG GGC CTA	144
Ser Pro Ala Gly Gly Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu	
35 40 45	
CTT GGT TGC ATC ATC ACT AGC CTT ACA GGC CGG GAC AAG AAC CAG GTC	192
Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val	
50 55 60	
GAG GGA GAG GTT CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG	240
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala	
65 70 75 80	
ACC TGC GTC AAC GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA	288
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser	
85 90 95	
AAG ACC TTA GCC GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT	336
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn	
100 105 110	
GTG GAC CAG GAC CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC	384
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser	
115 120 125	
TTG ACA CCA TGC ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA	432
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg	
130 135 140	
CAT GCT GAC GTC ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC	480
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser	
145 150 155 160	
CTG CTC TCC CCC AGG CCT GTC TCC TAC TTG AAG GGC TCT TCG GGT GGT	528
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly	
165 170 175	
CCA CTG CTC TGC CCT TCG GGG CAC GCT GTG GGC ATC TTC CGG GCT GCC	576
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala	

[illegible]

(2) INFORMATION FOR SEQ ID NO:101:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 651 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
(B) LOCATION: 1..651

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

ATG	GGC	AGC	AGC	CAT	CAT	CAT	CAT	CAT	CAC	AGC	AGC	GGC	CTG	GTG	CCG	48
Met	Gly	Ser	Ser	His	His	His	His	His	His	Ser	Ser	Gly	Leu	Val	Pro	
1				5					10					15		
CGC	GGC	AGC	CAT	ATG	GGT	TCT	GTT	GTT	ATT	GTT	GGT	AGA	ATT	ATT	TTA	96
Arg	Gly	Ser	His	Met	Gly	Ser	Val	Val	Ile	Val	Gly	Arg	Ile	Ile	Leu	
			20					25					30			
TCT	CCT	GCT	GGT	GGT	ATC	ACG	GCC	TAC	TCC	CAA	CAG	ACG	CGG	GGC	CTA	144
Ser	Pro	Ala	Gly	Gly	Ile	Thr	Ala	Tyr	Ser	Gln	Gln	Thr	Arg	Gly	Leu	
		35					40					45				
CTT	GGT	TGC	AAG	ATC	ACT	AGC	CTT	ACA	GGC	CGG	GAC	AAG	AAC	CAG	GTC	192
Leu	Gly	Cys	Lys	Ile	Thr	Ser	Leu	Thr	Gly	Arg	Asp	Lys	Asn	Gln	Val	
	50					55					60					
GAG	GGA	GAG	GTT	CAG	GTG	GTT	TCC	ACC	GCA	ACA	CAA	TCC	TTC	CTG	GCG	240
Glu	Gly	Glu	Val	Gln	Val	Val	Ser	Thr	Ala	Thr	Gln	Ser	Phe	Leu	Ala	
	65				70					75					80	
ACC	TGC	GTC	AAC	GGC	GTG	TGT	TGG	ACC	GTT	TAC	CAT	GGT	GCT	GGC	TCA	288
Thr	Cys	Val	Asn	Gly	Val	Cys	Trp	Thr	Val	Tyr	His	Gly	Ala	Gly	Ser	
				85					90					95		
AAG	ACC	TTA	GCC	GGC	CCA	AAG	GGG	CCA	ATC	ACC	CAG	ATG	TAC	ACT	AAT	336
Lys	Thr	Leu	Ala	Gly	Pro	Lys	Gly	Pro	Ile	Thr	Gln	Met	Tyr	Thr	Asn	
			100					105					110			

GTG GAC CAG GAC CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC	384
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser	
115 120 125	
TTG ACA CCA TGC ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA	432
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg	
130 135 140	
CAT GCT GAC GTC ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC	480
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser	
145 150 155 160	
CTG CTC TCC CCC AGG CCT GTC TCC TAC TTG AAG GGC TCT TCG GGT GGT	528
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly	
165 170 175	
CCA CTG CTC TGC CCT TCG GGG CAC GCT GTG GGC ATC TTC CGG GCT GCC	576
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala	
180 185 190	
GTA TGC ACC CGG GGG GTT GCG AAG GCG GTG GAC TTT GTG CCC GTA GAG	624
Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu	
195 200 205	
TCC ATG GAA ACT ACT ATG CGG TCT TGA	651
Ser Met Glu Thr Thr Met Arg Ser *	
210 215	

(2) INFORMATION FOR SEQ ID NO:102:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1998 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

ATG GGC AGC AGC CAT CAT CAT CAT CAT CAC AGC AGC GGC CTG GTG CCG	48
Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro	
1 5 10 15	
CGC GGC AGC CAT ATG GGT TCT GTT GTT ATT GTT GGT AGA ATT ATT TTA	96
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu	
20 25 30	
TCT GGT AGT GGT AGT ATC ACG GCC TAC TCC CAA CAG ACG CGG GGC CTA	144
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu	

35	40	45	
CTT GGT TGC ATC ATC ACT AGC CTT ACA GGC CGG GAC AAG AAC CAG GTC Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val 50 55 60			192
GAG GGA GAG GTT CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala 65 70 75 80			240
ACC TGC GTC AAC GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser 85 90 95			288
AAG ACC TTA GCC GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn 100 105 110			336
GTG GAC CAG GAC CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser 115 120 125			384
TTG ACA CCA TGC ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg 130 135 140			432
CAT GCT GAC GTC ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser 145 150 155 160			480
CTG CTC TCC CCC AGG CCT GTC TCC TAC TTG AAG GGC TCT TCG GGT GGT Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly 165 170 175			528
CCA CTG CTC TGC CCT TCG GGG CAC GCT GTG GGC ATC TTC CGG GCT GCC Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala 180 185 190			576
GTA TGC ACC CGG GGG GTT GCG AAG GCG GTG GAC TTT GTG CCC GTA GAG Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu 195 200 205			624
TCC ATG GAA ACT ACT ATG CGG TCT CCG GTC TTC ACG GAC AAC TCA TCC Ser Met Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser 210 215 220			672
CCC CCG GCC GTA CCG CAG TCA TTT CAA GTG GCC CAC CTA CAC GCT CCC Pro Pro Ala Val Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro 225 230 235 240			720
ACT GGC AGC GGC AAG AGT ACT AAA GTG CCG GCT GCA TAT GCA GCC CAA Thr Gly Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln 245 250 255			768
GGG TAC AAG GTG CTC GTC CTC AAT CCG TCC GTT GCC GCT ACC TTA GGG Gly Tyr Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly 260 265 270			816

SUBSTITUTE SHEET (rule 26)

TTT GGG GCG TAT ATG TCT AAG GCA CAC GGT ATT GAC CCC AAC ATC AGA Phe Gly Ala Tyr Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg 275 280 285	864
ACT GGG GTA AGG ACC ATT ACC ACA GGC GCC CCC GTC ACA TAC TCT ACC Thr Gly Val Arg Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr 290 295 300	912
TAT GGC AAG TTT CTT GCC GAT GGT GGT TGC TCT GGG GGC GCT TAT GAC Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp 305 310 315 320	960
ATC ATA ATA TGT GAT GAG TGC CAT TCA ACT GAC TCG ACT ACA ATC TTG Ile Ile Ile Cys Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu 325 330 335	1008
GGC ATC GGC ACA GTC CTG GAC CAA GCG GAG ACG GCT GGA GCG CGG CTT Gly Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu 340 345 350	1056
GTC GTG CTC GCC ACC GCT ACG CCT CCG GGA TCG GTC ACC GTG CCA CAC Val Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His 355 360 365	1104
CCA AAC ATC GAG GAG GTG GCC CTG TCT AAT ACT GGA GAG ATC CCC TTC Pro Asn Ile Glu Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe 370 375 380	1152
TAT GGC AAA GCC ATC CCC ATT GAA GCC ATC AGG GGG GGA AGG CAT CTC Tyr Gly Lys Ala Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu 385 390 395 400	1200
ATT TTC TGT CAT TCC AAG AAG AAG TGC GAC GAG CTC GCC GCA AAG CTG Ile Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu 405 410 415	1248
TCA GGC CTC GGA ATC AAC GCT GTG GCG TAT TAC CGG GGG CTC GAT GTG Ser Gly Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val 420 425 430	1296
TCC GTC ATA CCA ACT ATC GGA GAC GTC GTT GTC GTG GCA ACA GAC GCT Ser Val Ile Pro Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala 435 440 445	1344
CTG ATG ACG GGC TAT ACG GGC GAC TTT GAC TCA GTG ATC GAC TGT AAC Leu Met Thr Gly Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn 450 455 460	1392
ACA TGT GTC ACC CAG ACA GTC GAC TTC AGC TTG GAT CCC ACC TTC ACC Thr Cys Val Thr Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr 465 470 475 480	1440
ATT GAG ACG ACG ACC GTG CCT CAA GAC GCA GTG TCG CGC TCG CAG CGG Ile Glu Thr Thr Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg 485 490 495	1488
CGG GGT AGG ACT GGC AGG GGT AGG AGA GGC ATC TAC AGG TTT GTG ACT Arg Gly Arg Thr Gly Arg Gly Arg Arg Gly Ile Tyr Arg Phe Val Thr 1536	

SUBSTITUTE SHEET (rule 26)

500	505	510	
CCG GGA GAA CGG CCC TCG GGC ATG TTC GAT TCC TCG GTC CTG TGT GAG Pro Gly Glu Arg Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu 515 520 525			1584
TGC TAT GAC GCG GGC TGT GCT TGG TAC GAG CTC ACC CCC GCC GAG ACC Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr 530 535 540			1632
TCG GTT AGG TTG CGG GCC TAC CTG AAC ACA CCA GGG TTG CCC GTT TGC Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys 545 550 555 560			1680
CAG GAC CAC CTG GAG TTC TGG GAG AGT GTC TTC ACA GGC CTC ACC CAT Gln Asp His Leu Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His 565 570 575			1728
ATA GAT GCA CAC TTC TTG TCC CAG ACC AAG CAG GCA GGA GAC AAC TTC Ile Asp Ala His Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe 580 585 590			1776
CCC TAC CTG GTA GCA TAC CAA GCC ACG GTG TGC GCC AGG GCT CAG GCC Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala 595 600 605			1824
CCA CCT CCA TCA TGG GAT CAA ATG TGG AAG TGT CTC ATA CGG CTG AAA Pro Pro Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys 610 615 620			1872
CCT ACG CTG CAC GGG CCA ACA CCC TTG CTG TAC AGG CTG GGA GCC GTC Pro Thr Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val 625 630 635 640			1920
CAA AAT GAG GTC ACC CTC ACC CAC CCC ATA ACC AAA TAC ATC ATG GCA Gln Asn Glu Val Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala 645 650 655			1968
TGC ATG TCG GCT GAC CTG GAG GTC GTC ACT Cys Met Ser Ala Asp Leu Glu Val Val 660 665			1998

(2) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1998 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1997

SUBSTITUTE SHEET (rule 26)

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

ATG GGC AGC AGC CAT CAT CAT CAT CAT CAC AGC AGC GGC CTG GTG CCG	48
Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro	
1 5 10 15	
CGC GGC AGC CAT ATG GGT TCT GTT GTT ATT GTT GGT AGA ATT ATT TTA	96
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu	
20 25 30	
TCT GGT AGT GGT AGT ATC ACG GCC TAC TCC CAA CAG ACG CGG GGC CTA	144
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu	
35 40 45	
CTT GGT TGC AAG ATC ACT AGC CTT ACA GGC CGG GAC AAG AAC CAG GTC	192
Leu Gly Cys Lys Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val	
50 55 60	
GAG GGA GAG GTT CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG	240
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala	
65 70 75 80	
ACC TGC GTC AAC GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA	288
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser	
85 90 95	
AAG ACC TTA GCC GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT	336
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn	
100 105 110	
GTG GAC CAG GAC CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC	384
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser	
115 120 125	
TTG ACA CCA TGC ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA	432
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg	
130 135 140	
CAT GCT GAC GTC ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC	480
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser	
145 150 155 160	
CTG CTC TCC CCC AGG CCT GTC TCC TAC TTG AAG GGC TCT TCG GGT GGT	528
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly	
165 170 175	
CCA CTG CTC TGC CCT TCG GGG CAC GCT GTG GGC ATC TTC CGG GCT GCC	576
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala	
180 185 190	
GTA TGC ACC CGG GGG GTT GCG AAG GCG GTG GAC TTT GTG CCC GTA GAG	624
Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu	

195	200	205	
TCC ATG GAA ACT ACT ATG CGG TCT CCG GTC TTC ACG GAC AAC TCA TCC Ser Met Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser 210 215 220			672
CCC CCG GCC GTA CCG CAG TCA TTT CAA GTG GCC CAC CTA CAC GCT CCC Pro Pro Ala Val Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro 225 230 235 240			720
ACT GGC AGC GGC AAG AGT ACT AAA GTG CCG GCT GCA TAT GCA GCC CAA Thr Gly Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln 245 250 255			768
GGG TAC AAG GTG CTC GTC CTC AAT CCG TCC GTT GCC GCT ACC TTA GGG Gly Tyr Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly 260 265 270			816
TTT GGG GCG TAT ATG TCT AAG GCA CAC GGT ATT GAC CCC AAC ATC AGA Phe Gly Ala Tyr Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg 275 280 285			864
ACT GGG GTA AGG ACC ATT ACC ACA GGC GCC CCC GTC ACA TAC TCT ACC Thr Gly Val Arg Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr 290 295 300			912
TAT GGC AAG TTT CTT GCC GAT GGT GGT TGC TCT GGG GGC GCT TAT GAC Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp 305 310 315 320			960
ATC ATA ATA TGT GAT GAG TGC CAT TCA ACT GAC TCG ACT ACA ATC TTG Ile Ile Ile Cys Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu 325 330 335			1008
GGC ATC GGC ACA GTC CTG GAC CAA GCG GAG ACG GCT GGA GCG CGG CTT Gly Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu 340 345 350			1056
GTC GTG CTC GCC ACC GCT ACG CCT CCG GGA TCG GTC ACC GTG CCA CAC Val Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His 355 360 365			1104
CCA AAC ATC GAG GAG GTG GCC CTG TCT AAT ACT GGA GAG ATC CCC TTC Pro Asn Ile Glu Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe 370 375 380			1152
TAT GGC AAA GCC ATC CCC ATT GAA GCC ATC AGG GGG GGA AGG CAT CTC Tyr Gly Lys Ala Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu 385 390 395 400			1200
ATT TTC TGT CAT TCC AAG AAG AAG TGC GAC GAG CTC GCC GCA AAG CTG Ile Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu 405 410 415			1248
TCA GGC CTC GGA ATC AAC GCT GTG GCG TAT TAC CGG GGG CTC GAT GTG Ser Gly Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val 420 425 430			1296

SUBSTITUTE SHEET (rule 26)

TCC	GTC	ATA	CCA	ACT	ATC	GGA	GAC	GTC	GTT	GTC	GTG	GCA	ACA	GAC	GCT	1344
Ser	Val	Ile	Pro	Thr	Ile	Gly	Asp	Val	Val	Val	Val	Ala	Thr	Asp	Ala	
		435					440						445			
CTG	ATG	ACG	GGC	TAT	ACG	GGC	GAC	TTT	GAC	TCA	GTG	ATC	GAC	TGT	AAC	1392
Leu	Met	Thr	Gly	Tyr	Thr	Gly	Asp	Phe	Asp	Ser	Val	Ile	Asp	Cys	Asn	
		450					455					460				
ACA	TGT	GTC	ACC	CAG	ACA	GTC	GAC	TTC	AGC	TTG	GAT	CCC	ACC	TTC	ACC	1440
Thr	Cys	Val	Thr	Gln	Thr	Val	Asp	Phe	Ser	Leu	Asp	Pro	Thr	Phe	Thr	
		465				470					475				480	
ATT	GAG	ACG	ACG	ACC	GTG	CCT	CAA	GAC	GCA	GTG	TCG	CGC	TCG	CAG	CGG	1488
Ile	Glu	Thr	Thr	Thr	Val	Pro	Gln	Asp	Ala	Val	Ser	Arg	Ser	Gln	Arg	
				485					490					495		
CGG	GGT	AGG	ACT	GGC	AGG	GGT	AGG	AGA	GGC	ATC	TAC	AGG	TTT	GTG	ACT	1536
Arg	Gly	Arg	Thr	Gly	Arg	Gly	Arg	Arg	Gly	Ile	Tyr	Arg	Phe	Val	Thr	
			500					505					510			
CCG	GGA	GAA	CGG	CCC	TCG	GGC	ATG	TTC	GAT	TCC	TCG	GTC	CTG	TGT	GAG	1584
Pro	Gly	Glu	Arg	Pro	Ser	Gly	Met	Phe	Asp	Ser	Ser	Val	Leu	Cys	Glu	
		515					520					525				
TGC	TAT	GAC	GCG	GGC	TGT	GCT	TGG	TAC	GAG	CTC	ACC	CCC	GCC	GAG	ACC	1632
Cys	Tyr	Asp	Ala	Gly	Cys	Ala	Trp	Tyr	Glu	Leu	Thr	Pro	Ala	Glu	Thr	
		530					535					540				
TCG	GTT	AGG	TTG	CGG	GCC	TAC	CTG	AAC	ACA	CCA	GGG	TTG	CCC	GTT	TGC	1680
Ser	Val	Arg	Leu	Arg	Ala	Tyr	Leu	Asn	Thr	Pro	Gly	Leu	Pro	Val	Cys	
					550					555					560	
CAG	GAC	CAC	CTG	GAG	TTC	TGG	GAG	AGT	GTC	TTC	ACA	GGC	CTC	ACC	CAT	1728
Gln	Asp	His	Leu	Glu	Phe	Trp	Glu	Ser	Val	Phe	Thr	Gly	Leu	Thr	His	
				565					570					575		
ATA	GAT	GCA	CAC	TTC	TTG	TCC	CAG	ACC	AAG	CAG	GCA	GGA	GAC	AAC	TTC	1776
Ile	Asp	Ala	His	Phe	Leu	Ser	Gln	Thr	Lys	Gln	Ala	Gly	Asp	Asn	Phe	
			580					585					590			
CCC	TAC	CTG	GTA	GCA	TAC	CAA	GCC	ACG	GTG	TGC	GCC	AGG	GCT	CAG	GCC	1824
Pro	Tyr	Leu	Val	Ala	Tyr	Gln	Ala	Thr	Val	Cys	Ala	Arg	Ala	Gln	Ala	
			595				600					605				
CCA	CCT	CCA	TCA	TGG	GAT	CAA	ATG	TGG	AAG	TGT	CTC	ATA	CGG	CTG	AAA	1872
Pro	Pro	Pro	Ser	Trp	Asp	Gln	Met	Trp	Lys	Cys	Leu	Ile	Arg	Leu	Lys	
		610					615					620				
CCT	ACG	CTG	CAC	GGG	CCA	ACA	CCC	TTG	CTG	TAC	AGG	CTG	GGA	GCC	GTC	1920
Pro	Thr	Leu	His	Gly	Pro	Thr	Pro	Leu	Leu	Tyr	Arg	Leu	Gly	Ala	Val	
		625				630				635					640	
CAA	AAT	GAG	GTC	ACC	CTC	ACC	CAC	CCC	ATA	ACC	AAA	TAC	ATC	ATG	GCA	1968
Gln	Asn	Glu	Val	Thr	Leu	Thr	His	Pro	Ile	Thr	Lys	Tyr	Ile	Met	Ala	
				645					650					655		
TGC	ATG	TCG	GCT	GAC	CTG	GAG	GTC	GTC	ACT							1998
Cys	Met	Ser	Ala	Asp	Leu	Glu	Val	Val								

SUBSTITUTE SHEET (rule 26)

660

665

(2) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1998 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

ATG GGC AGC AGC CAT CAT CAT CAT CAT CAC AGC AGC GGC CTG GTG CCG	48
Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro	
1 5 10 15	
CGC GGC AGC CAT ATG GGT TCT GTT GTT ATT GTT GGT AGA ATT ATT TTA	96
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu	
20 25 30	
TCT GGT AGT GGT AGT ATC ACG GCC TAC TCC CAA CAG ACG CGG GGC CTA	144
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu	
35 40 45	
CTT GGT TGC ATC AAG ACT AGC CTT ACA GGC CGG GAC AAG AAC CAG GTC	192
Leu Gly Cys Ile Lys Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val	
50 55 60	
GAG GGA GAG GTT CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG	240
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala	
65 70 75 80	
ACC TGC GTC AAC GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA	288
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser	
85 90 95	
AAG ACC TTA GCC GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT	336
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn	
100 105 110	
GTG GAC CAG GAC CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC	384
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser	
115 120 125	
TTG ACA CCA TGC ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA	432
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg	
130 135 140	

CAT	GCT	GAC	GTC	ATT	CCG	GTG	CGC	CGG	CGG	GGC	GAC	AGT	AGG	GGG	AGC	480
His	Ala	Asp	Val	Ile	Pro	Val	Arg	Arg	Arg	Gly	Asp	Ser	Arg	Gly	Ser	
145					150					155					160	
CTG	CTC	TCC	CCC	AGG	CCT	GTC	TCC	TAC	TTG	AAG	GGC	TCT	TCG	GGT	GGT	528
Leu	Leu	Ser	Pro	Arg	Pro	Val	Ser	Tyr	Leu	Lys	Gly	Ser	Ser	Gly	Gly	
				165					170					175		
CCA	CTG	CTC	TGC	CCT	TCG	GGG	CAC	GCT	GTG	GGC	ATC	TTC	CGG	GCT	GCC	576
Pro	Leu	Leu	Cys	Pro	Ser	Gly	His	Ala	Val	Gly	Ile	Phe	Arg	Ala	Ala	
			180					185					190			
GTA	TGC	ACC	CGG	GGG	GTT	GCG	AAG	GCG	GTG	GAC	TTT	GTG	CCC	GTA	GAG	624
Val	Cys	Thr	Arg	Gly	Val	Ala	Lys	Ala	Val	Asp	Phe	Val	Pro	Val	Glu	
		195					200					205				
TCC	ATG	GAA	ACT	ACT	ATG	CGG	TCT	CCG	GTC	TTC	ACG	GAC	AAC	TCA	TCC	672
Ser	Met	Glu	Thr	Thr	Met	Arg	Ser	Pro	Val	Phe	Thr	Asp	Asn	Ser	Ser	
	210					215					220					
CCC	CCG	GCC	GTA	CCG	CAG	TCA	TTT	CAA	GTG	GCC	CAC	CTA	CAC	GCT	CCC	720
Pro	Pro	Ala	Val	Pro	Gln	Ser	Phe	Gln	Val	Ala	His	Leu	His	Ala	Pro	
225					230					235					240	
ACT	GGC	AGC	GGC	AAG	AGT	ACT	AAA	GTG	CCG	GCT	GCA	TAT	GCA	GCC	CAA	768
Thr	Gly	Ser	Gly	Lys	Ser	Thr	Lys	Val	Pro	Ala	Ala	Tyr	Ala	Ala	Gln	
				245					250				255			
GGG	TAC	AAG	GTG	CTC	GTC	CTC	AAT	CCG	TCC	GTT	GCC	GCT	ACC	TTA	GGG	816
Gly	Tyr	Lys	Val	Leu	Val	Leu	Asn	Pro	Ser	Val	Ala	Ala	Thr	Leu	Gly	
			260					265					270			
TTT	GGG	GCG	TAT	ATG	TCT	AAG	GCA	CAC	GGT	ATT	GAC	CCC	AAC	ATC	AGA	864
Phe	Gly	Ala	Tyr	Met	Ser	Lys	Ala	His	Gly	Ile	Asp	Pro	Asn	Ile	Arg	
		275					280					285				
ACT	GGG	GTA	AGG	ACC	ATT	ACC	ACA	GGC	GCC	CCC	GTC	ACA	TAC	TCT	ACC	912
Thr	Gly	Val	Arg	Thr	Ile	Thr	Thr	Gly	Ala	Pro	Val	Thr	Tyr	Ser	Thr	
		290				295					300					
TAT	GGC	AAG	TTT	CTT	GCC	GAT	GGT	GGT	TGC	TCT	GGG	GGC	GCT	TAT	GAC	960
Tyr	Gly	Lys	Phe	Leu	Ala	Asp	Gly	Gly	Cys	Ser	Gly	Gly	Ala	Tyr	Asp	
305					310					315					320	
ATC	ATA	ATA	TGT	GAT	GAG	TGC	CAT	TCA	ACT	GAC	TCG	ACT	ACA	ATC	TTG	1008
Ile	Ile	Ile	Cys	Asp	Glu	Cys	His	Ser	Thr	Asp	Ser	Thr	Thr	Ile	Leu	
				325					330					335		
GGC	ATC	GGC	ACA	GTC	CTG	GAC	CAA	GCG	GAG	ACG	GCT	GGA	GCG	CGG	CTT	1056
Gly	Ile	Gly	Thr	Val	Leu	Asp	Gln	Ala	Glu	Thr	Ala	Gly	Ala	Arg	Leu	
			340					345					350			
GTC	GTG	CTC	GCC	ACC	GCT	ACG	CCT	CCG	GGA	TCG	GTC	ACC	GTG	CCA	CAC	1104
Val	Val	Leu	Ala	Thr	Ala	Thr	Pro	Pro	Gly	Ser	Val	Thr	Val	Pro	His	
			355				360					365				
CCA	AAC	ATC	GAG	GAG	GTG	GCC	CTG	TCT	AAT	ACT	GGA	GAG	ATC	CCC	TTC	1152
Pro	Asn	Ile	Glu	Glu	Val	Ala	Leu	Ser	Asn	Thr	Gly	Glu	Ile	Pro	Phe	

370	375	380	
TAT GGC AAA GCC ATC CCC ATT GAA GCC ATC AGG GGG GGA AGG CAT CTC			1200
Tyr Gly Lys Ala Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu			
385	390	395	400
ATT TTC TGT CAT TCC AAG AAG AAG TGC GAC GAG CTC GCC GCA AAG CTG			1248
Ile Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu			
405	410		415
TCA GGC CTC GGA ATC AAC GCT GTG GCG TAT TAC CGG GGG CTC GAT GTG			1296
Ser Gly Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val			
420	425		430
TCC GTC ATA CCA ACT ATC GGA GAC GTC GTT GTC GTG GCA ACA GAC GCT			1344
Ser Val Ile Pro Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala			
435	440		445
CTG ATG ACG GGC TAT ACG GGC GAC TTT GAC TCA GTG ATC GAC TGT AAC			1392
Leu Met Thr Gly Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn			
450	455		460
ACA TGT GTC ACC CAG ACA GTC GAC TTC AGC TTG GAT CCC ACC TTC ACC			1440
Thr Cys Val Thr Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr			
465	470		475
ATT GAG ACG ACG ACC GTG CCT CAA GAC GCA GTG TCG CGC TCG CAG CGG			1488
Ile Glu Thr Thr Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg			
485	490		495
CGG GGT AGG ACT GGC AGG GGT AGG AGA GGC ATC TAC AGG TTT GTG ACT			1536
Arg Gly Arg Thr Gly Arg Gly Arg Gly Ile Tyr Arg Phe Val Thr			
500	505		510
CCG GGA GAA CGG CCC TCG GGC ATG TTC GAT TCC TCG GTC CTG TGT GAG			1584
Pro Gly Glu Arg Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu			
515	520		525
TGC TAT GAC GCG GGC TGT GCT TGG TAC GAG CTC ACC CCC GCC GAG ACC			1632
Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr			
530	535		540
TCG GTT AGG TTG CGG GCC TAC CTG AAC ACA CCA GGG TTG CCC GTT TGC			1680
Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys			
545	550		555
CAG GAC CAC CTG GAG TTC TGG GAG AGT GTC TTC ACA GGC CTC ACC CAT			1728
Gln Asp His Leu Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His			
565	570		575
ATA GAT GCA CAC TTC TTG TCC CAG ACC AAG CAG GCA GGA GAC AAC TTC			1776
Ile Asp Ala His Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe			
580	585		590
CCC TAC CTG GTA GCA TAC CAA GCC ACG GTG TGC GCC AGG GCT CAG GCC			1824
Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala			
595	600		605

CCA	CCT	CCA	TCA	TGG	GAT	CAA	ATG	TGG	AAG	TGT	CTC	ATA	CGG	CTG	AAA	1872
Pro	Pro	Pro	Ser	Trp	Asp	Gln	Met	Trp	Lys	Cys	Leu	Ile	Arg	Leu	Lys	
610						615					620					
CCT	ACG	CTG	CAC	GGG	CCA	ACA	CCC	TTG	CTG	TAC	AGG	CTG	GGA	GCC	GTC	1920
Pro	Thr	Leu	His	Gly	Pro	Thr	Pro	Leu	Leu	Tyr	Arg	Leu	Gly	Ala	Val	
625					630					635					640	
CAA	AAT	GAG	GTC	ACC	CTC	ACC	CAC	CCC	ATA	ACC	AAA	TAC	ATC	ATG	GCA	1968
Gln	Asn	Glu	Val	Thr	Leu	Thr	His	Pro	Ile	Thr	Lys	Tyr	Ile	Met	Ala	
				645					650						655	
TGC	ATG	TCG	GCT	GAC	CTG	GAG	GTC	GTC	ACT							1998
Cys	Met	Ser	Ala	Asp	Leu	Glu	Val	Val								
			660					665								

(2) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1998 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

ATG	GGC	AGC	AGC	CAT	CAT	CAT	CAT	CAT	CAC	AGC	AGC	GGC	CTG	GTG	CCG	48
Met	Gly	Ser	Ser	His	His	His	His	His	His	Ser	Ser	Gly	Leu	Val	Pro	
1				5				10					15			
CGC	GGC	AGC	CAT	ATG	GGT	TCT	GTT	GTT	ATT	GTT	GGT	AGA	ATT	ATT	TTA	96
Arg	Gly	Ser	His	Met	Gly	Ser	Val	Val	Ile	Val	Gly	Arg	Ile	Ile	Leu	
			20				25					30				
TCT	GGT	AGT	GGT	AGT	ATC	ACG	GCC	TAC	TCC	CAA	CAG	ACG	CGG	GGC	CTA	144
Ser	Gly	Ser	Gly	Ser	Ile	Thr	Ala	Tyr	Ser	Gln	Gln	Thr	Arg	Gly	Leu	
		35				40					45					
CTT	GGT	TGC	AAG	AAG	ACT	AGC	CTT	ACA	GGC	CGG	GAC	AAG	AAC	CAG	GTC	192
Leu	Gly	Cys	Lys	Lys	Thr	Ser	Leu	Thr	Gly	Arg	Asp	Lys	Asn	Gln	Val	
	50					55				60						
GAG	GGA	GAG	GTT	CAG	GTG	GTT	TCC	ACC	GCA	ACA	CAA	TCC	TTC	CTG	GCG	240
Glu	Gly	Glu	Val	Gln	Val	Val	Ser	Thr	Ala	Thr	Gln	Ser	Phe	Leu	Ala	
65					70				75					80		
ACC	TGC	GTC	AAC	GGC	GTG	TGT	TGG	ACC	GTT	TAC	CAT	GGT	GCT	GGC	TCA	288
Thr	Cys	Val	Asn	Gly	Val	Cys	Trp	Thr	Val	Tyr	His	Gly	Ala	Gly	Ser	

85	90	95	
AAG ACC TTA GCC GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn 100 105 110			336
GTG GAC CAG GAC CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser 115 120 125			384
TTG ACA CCA TGC ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg 130 135 140			432
CAT GCT GAC GTC ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser 145 150 155 160			480
CTG CTC TCC CCC AGG CCT GTC TCC TAC TTG AAG GGC TCT TCG GGT GGT Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly 165 170 175			528
CCA CTG CTC TGC CCT TCG GGG CAC GCT GTG GGC ATC TTC CGG GCT GCC Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala 180 185 190			576
GTA TGC ACC CGG GGG GTT GCG AAG GCG GTG GAC TTT GTG CCC GTA GAG Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu 195 200 205			624
TCC ATG GAA ACT ACT ATG CGG TCT CCG GTC TTC ACG GAC AAC TCA TCC Ser Met Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser 210 215 220			672
CCC CCG GCC GTA CCG CAG TCA TTT CAA GTG GCC CAC CTA CAC GCT CCC Pro Pro Ala Val Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro 225 230 235 240			720
ACT GGC AGC GGC AAG AGT ACT AAA GTG CCG GCT GCA TAT GCA GCC CAA Thr Gly Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln 245 250 255			768
GGG TAC AAG GTG CTC GTC CTC AAT CCG TCC GTT GCC GCT ACC TTA GGG Gly Tyr Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly 260 265 270			816
TTT GGG GCG TAT ATG TCT AAG GCA CAC GGT ATT GAC CCC AAC ATC AGA Phe Gly Ala Tyr Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg 275 280 285			864
ACT GGG GTA AGG ACC ATT ACC ACA GGC GCC CCC GTC ACA TAC TCT ACC Thr Gly Val Arg Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr 290 295 300			912
TAT GGC AAG TTT CTT GCC GAT GGT GGT TGC TCT GGG GGC GCT TAT GAC Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp 305 310 315 320			960

ATC	ATA	ATA	TGT	GAT	GAG	TGC	CAT	TCA	ACT	GAC	TCG	ACT	ACA	ATC	TTG	1008
Ile	Ile	Ile	Cys	Asp	Glu	Cys	His	Ser	Thr	Asp	Ser	Thr	Thr	Ile	Leu	
			325						330					335		
GGC	ATC	GGC	ACA	GTC	CTG	GAC	CAA	GCG	GAG	ACG	GCT	GGA	GCG	CGG	CTT	1056
Gly	Ile	Gly	Thr	Val	Leu	Asp	Gln	Ala	Glu	Thr	Ala	Gly	Ala	Arg	Leu	
			340					345					350			
GTC	GTG	CTC	GCC	ACC	GCT	ACG	CCT	CCG	GGA	TCG	GTC	ACC	GTG	CCA	CAC	1104
Val	Val	Leu	Ala	Thr	Ala	Thr	Pro	Pro	Gly	Ser	Val	Thr	Val	Pro	His	
		355					360					365				
CCA	AAC	ATC	GAG	GAG	GTG	GCC	CTG	TCT	AAT	ACT	GGA	GAG	ATC	CCC	TTC	1152
Pro	Asn	Ile	Glu	Glu	Val	Ala	Leu	Ser	Asn	Thr	Gly	Glu	Ile	Pro	Phe	
	370					375					380					
TAT	GGC	AAA	GCC	ATC	CCC	ATT	GAA	GCC	ATC	AGG	GGG	GGA	AGG	CAT	CTC	1200
Tyr	Gly	Lys	Ala	Ile	Pro	Ile	Glu	Ala	Ile	Arg	Gly	Gly	Arg	His	Leu	
385					390					395					400	
ATT	TTC	TGT	CAT	TCC	AAG	AAG	AAG	TGC	GAC	GAG	CTC	GCC	GCA	AAG	CTG	1248
Ile	Phe	Cys	His	Ser	Lys	Lys	Lys	Cys	Asp	Glu	Leu	Ala	Ala	Lys	Leu	
				405					410					415		
TCA	GGC	CTC	GGA	ATC	AAC	GCT	GTG	GCG	TAT	TAC	CGG	GGG	CTC	GAT	GTG	1296
Ser	Gly	Leu	Gly	Ile	Asn	Ala	Val	Ala	Tyr	Tyr	Arg	Gly	Leu	Asp	Val	
		420					425						430			
TCC	GTC	ATA	CCA	ACT	ATC	GGA	GAC	GTC	GTT	GTC	GTG	GCA	ACA	GAC	GCT	1344
Ser	Val	Ile	Pro	Thr	Ile	Gly	Asp	Val	Val	Val	Val	Ala	Thr	Asp	Ala	
		435				440						445				
CTG	ATG	ACG	GGC	TAT	ACG	GGC	GAC	TTT	GAC	TCA	GTG	ATC	GAC	TGT	AAC	1392
Leu	Met	Thr	Gly	Tyr	Thr	Gly	Asp	Phe	Asp	Ser	Val	Ile	Asp	Cys	Asn	
	450					455					460					
ACA	TGT	GTC	ACC	CAG	ACA	GTC	GAC	TTC	AGC	TTG	GAT	CCC	ACC	TTC	ACC	1440
Thr	Cys	Val	Thr	Gln	Thr	Val	Asp	Phe	Ser	Leu	Asp	Pro	Thr	Phe	Thr	
465					470					475				480		
ATT	GAG	ACG	ACG	ACC	GTG	CCT	CAA	GAC	GCA	GTG	TCG	CGC	TCG	CAG	CGG	1488
Ile	Glu	Thr	Thr	Thr	Val	Pro	Gln	Asp	Ala	Val	Ser	Arg	Ser	Gln	Arg	
				485				490						495		
CGG	GGT	AGG	ACT	GGC	AGG	GGT	AGG	AGA	GGC	ATC	TAC	AGG	TTT	GTG	ACT	1536
Arg	Gly	Arg	Thr	Gly	Arg	Gly	Arg	Arg	Gly	Ile	Tyr	Arg	Phe	Val	Thr	
		500					505						510			
CCG	GGA	GAA	CGG	CCC	TCG	GGC	ATG	TTC	GAT	TCC	TCG	GTC	CTG	TGT	GAG	1584
Pro	Gly	Glu	Arg	Pro	Ser	Gly	Met	Phe	Asp	Ser	Ser	Val	Leu	Cys	Glu	
		515				520						525				
TGC	TAT	GAC	GCG	GGC	TGT	GCT	TGG	TAC	GAG	CTC	ACC	CCC	GCC	GAG	ACC	1632
Cys	Tyr	Asp	Ala	Gly	Cys	Ala	Trp	Tyr	Glu	Leu	Thr	Pro	Ala	Glu	Thr	
	530					535					540					
TCG	GTT	AGG	TTG	CGG	GCC	TAC	CTG	AAC	ACA	CCA	GGG	TTG	CCC	GTT	TGC	1680
Ser	Val	Arg	Leu	Arg	Ala	Tyr	Leu	Asn	Thr	Pro	Gly	Leu	Pro	Val	Cys	

545	550	555	560	
CAG GAC CAC CTG GAG TTC TGG GAG AGT GTC TTC ACA GGC CTC ACC CAT				1728
Gln Asp His Leu Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His				
565		570	575	
ATA GAT GCA CAC TTC TTG TCC CAG ACC AAG CAG GCA GGA GAC AAC TTC				1776
Ile Asp Ala His Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe				
580	585	590		
CCC TAC CTG GTA GCA TAC CAA GCC ACG GTG TGC GCC AGG GCT CAG GCC				1824
Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala				
595	600	605		
CCA CCT CCA TCA TGG GAT CAA ATG TGG AAG TGT CTC ATA CGG CTG AAA				1872
Pro Pro Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys				
610	615	620		
CCT ACG CTG CAC GGG CCA ACA CCC TTG CTG TAC AGG CTG GGA GCC GTC				1920
Pro Thr Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val				
625	630	635	640	
CAA AAT GAG GTC ACC CTC ACC CAC CCC ATA ACC AAA TAC ATC ATG GCA				1968
Gln Asn Glu Val Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala				
645	650	655		
TGC ATG TCG GCT GAC CTG GAG GTC GTC ACT				1998
Cys Met Ser Ala Asp Leu Glu Val Val				
660	665			

(2) INFORMATION FOR SEQ ID NO:106:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1998 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

ATG GGC AGC AGC CAT CAT CAT CAT CAT CAC AGC AGC GGC CTG GTG CCG	48
Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro	
1 5 10 15	
CGC GGC AGC CAT ATG GGT TCT GTT GTT ATT GTT GGT AGA ATT ATT TTA	96
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu	
20 25 30	
TCT GGT AGT GGT AGT ATC ACG GCC TAC TCC CAA CAG ACG CGG GGC CTA	144

Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu	
35 40 45	
CTT GGT TGC ATC ATC ACT AGC CTT ACA GGC CGG GAC AAG AAC CAG GTC	192
Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val	
50 55 60	
GAG GGA GAG GTT CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG	240
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala	
65 70 75 80	
ACC TGC GTC AAC GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA	288
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser	
85 90 95	
AAG ACC TTA GCC GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT	336
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn	
100 105 110	
GTG GAC CAG GAC CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC	384
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser	
115 120 125	
TTG ACA CCA TGC ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA	432
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg	
130 135 140	
CAT GCT GAC GTC ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC	480
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser	
145 150 155 160	
CTG CTC TCC CCC AGG CCT GTC TCC TAC TTG AAG GGC TCT GCT GGT GGT	528
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ala Gly Gly	
165 170 175	
CCA CTG CTC TGC CCT TCG GGC CAC GCT GTG GGC ATC TTC CGG GCT GCC	576
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala	
180 185 190	
GTA TGC ACC CGG GGG GTT GCG AAG GCG GTG GAC TTT GTG CCC GTA GAG	624
Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu	
195 200 205	
TCC ATG GAA ACT ACT ATG CGG TCT CCG GTC TTC ACG GAC AAC TCA TCC	672
Ser Met Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser	
210 215 220	
CCC CCG GCC GTA CCG CAG TCA TTT CAA GTG GCC CAC CTA CAC GCT CCC	720
Pro Pro Ala Val Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro	
225 230 235 240	
ACT GGC AGC GGC AAG AGT ACT AAA GTG CCG GCT GCA TAT GCA GCC CAA	768
Thr Gly Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln	
245 250 255	
GGG TAC AAG GTG CTC GTC CTC AAT CCG TCC GTT GCC GCT ACC TTA GGG	816
Gly Tyr Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly	
260 265 270	

SUBSTITUTE SHEET (rule 26)

TTT GGG GCG TAT ATG TCT AAG GCA CAC GGT ATT GAC CCC AAC ATC AGA Phe Gly Ala Tyr Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg 275 280 285	864
ACT GGG GTA AGG ACC ATT ACC ACA GGC GCC CCC GTC ACA TAC TCT ACC Thr Gly Val Arg Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr 290 295 300	912
TAT GGC AAG TTT CTT GCC GAT GGT GGT TGC TCT GGG GGC GCT TAT GAC Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp 305 310 315 320	960
ATC ATA ATA TGT GAT GAG TGC CAT TCA ACT GAC TCG ACT ACA ATC TTG Ile Ile Ile Cys Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu 325 330 335	1008
GGC ATC GGC ACA GTC CTG GAC CAA GCG GAG ACG GCT GGA GCG CGG CTT Gly Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu 340 345 350	1056
GTC GTG CTC GCC ACC GCT ACG CCT CCG GGA TCG GTC ACC GTG CCA CAC Val Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His 355 360 365	1104
CCA AAC ATC GAG GAG GTG GCC CTG TCT AAT ACT GGA GAG ATC CCC TTC Pro Asn Ile Glu Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe 370 375 380	1152
TAT GGC AAA GCC ATC CCC ATT GAA GCC ATC AGG GGG GGA AGG CAT CTC Tyr Gly Lys Ala Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu 385 390 395 400	1200
ATT TTC TGT CAT TCC AAG AAG AAG TGC GAC GAG CTC GCC GCA AAG CTG Ile Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu 405 410 415	1248
TCA GGC CTC GGA ATC AAC GCT GTG GCG TAT TAC CGG GGG CTC GAT GTG Ser Gly Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val 420 425 430	1296
TCC GTC ATA CCA ACT ATC GGA GAC GTC GTT GTC GTG GCA ACA GAC GCT Ser Val Ile Pro Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala 435 440 445	1344
CTG ATG ACG GGC TAT ACG GGC GAC TTT GAC TCA GTG ATC GAC TGT AAC Leu Met Thr Gly Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn 450 455 460	1392
ACA TGT GTC ACC CAG ACA GTC GAC TTC AGC TTG GAT CCC ACC TTC ACC Thr Cys Val Thr Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr 465 470 475 480	1440
ATT GAG ACG ACG ACC GTG CCT CAA GAC GCA GTG TCG CGC TCG CAG CGG Ile Glu Thr Thr Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg 485 490 495	1488
CGG GGT AGG ACT GGC AGG GGT AGG AGA GGC ATC TAC AGG TTT GTG ACT	1536

SUBSTITUTE SHEET (rule 26)

Arg Gly Arg Thr Gly Arg Gly Arg Arg Gly Ile Tyr Arg Phe Val Thr	
500 505 510	
CCG GGA GAA CGG CCC TCG GGC ATG TTC GAT TCC TCG GTC CTG TGT GAG	1584
Pro Gly Glu Arg Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu	
515 520 525	
TGC TAT GAC GCG GGC TGT GCT TGG TAC GAG CTC ACC CCC GCC GAG ACC	1632
Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr	
530 535 540	
TCG GTT AGG TTG CGG GCC TAC CTG AAC ACA CCA GGG TTG CCC GTT TGC	1680
Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys	
545 550 555 560	
CAG GAC CAC CTG GAG TTC TGG GAG AGT GTC TTC ACA GGC CTC ACC CAT	1728
Gln Asp His Leu Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His	
565 570 575	
ATA GAT GCA CAC TTC TTG TCC CAG ACC AAG CAG GCA GGA GAC AAC TTC	1776
Ile Asp Ala His Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe	
580 585 590	
CCC TAC CTG GTA GCA TAC CAA GCC ACG GTG TGC GCC AGG GCT CAG GCC	1824
Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala	
595 600 605	
CCA CCT CCA TCA TGG GAT CAA ATG TGG AAG TGT CTC ATA CGG CTG AAA	1872
Pro Pro Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys	
610 615 620	
CCT ACG CTG CAC GGG CCA ACA CCC TTG CTG TAC AGG CTG GGA GCC GTC	1920
Pro Thr Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val	
625 630 635 640	
CAA AAT GAG GTC ACC CTC ACC CAC CCC ATA ACC AAA TAC ATC ATG GCA	1968
Gln Asn Glu Val Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala	
645 650 655	
TGC ATG TCG GCT GAC CTG GAG GTC GTC ACT	1998
Cys Met Ser Ala Asp Leu Glu Val Val	
660 665	

(2) INFORMATION FOR SEQ ID NO:107:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1998 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1997

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

ATG GGC AGC AGC CAT CAT CAT CAT CAT CAC AGC AGC GGC CTG GTG CCG	48
Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro	
1 5 10 15	
CGC GGC AGC CAT ATG GGT TCT GTT GTT ATT GTT GGT AGA ATT ATT TTA	96
Arg Gly Ser His Met Gly Ser Val Ile Val Gly Arg Ile Ile Leu	
20 25 30	
TCT GGT AGT GGT AGT ATC ACG GCC TAC TCC CAA CAG ACG CGG GGC CTA	144
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu	
35 40 45	
CTT GGT TGC AAG ATC ACT AGC CTT ACA GGC CGG GAC AAG AAC CAG GTC	192
Leu Gly Cys Lys Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val	
50 55 60	
GAG GGA GAG GTT CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG	240
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala	
65 70 75 80	
ACC TGC GTC AAC GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA	288
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser	
85 90 95	
AAG ACC TTA GCC GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT	336
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn	
100 105 110	
GTG GAC CAG GAC CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC	384
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser	
115 120 125	
TTG ACA CCA TGC ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA	432
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg	
130 135 140	
CAT GCT GAC GTC ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC	480
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser	
145 150 155 160	
CTG CTC TCC CCC AGG CCT GTC TCC TAC TTG AAG GGC TCT GCT GGT GGT	528
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ala Gly Gly	
165 170 175	
CCA CTG CTC TGC CCT TCG GGG CAC GCT GTG GGC ATC TTC CGG GCT GCC	576
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala	
180 185 190	
GTA TGC ACC CGG GGG GTT GCG AAG GCG GTG GAC TTT GTG CCC GTA GAG	624
Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu	

195	200	205	
TCC ATG GAA ACT ACT ATG CGG TCT CCG GTC TTC ACG GAC AAC TCA TCC Ser Met Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser 210 215 220			672
CCC CCG GCC GTA CCG CAG TCA TTT CAA GTG GCC CAC CTA CAC GCT CCC Pro Pro Ala Val Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro 225 230 235 240			720
ACT GGC AGC GGC AAG AGT ACT AAA GTG CCG GCT GCA TAT GCA GCC CAA Thr Gly Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln 245 250 255			768
GGG TAC AAG GTG CTC GTC CTC AAT CCG TCC GTT GCC GCT ACC TTA GGG Gly Tyr Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly 260 265 270			816
TTT GGG GCG TAT ATG TCT AAG GCA CAC GGT ATT GAC CCC AAC ATC AGA Phe Gly Ala Tyr Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg 275 280 285			864
ACT GGG GTA AGG ACC ATT ACC ACA GGC GCC CCC GTC ACA TAC TCT ACC Thr Gly Val Arg Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr 290 295 300			912
TAT GGC AAG TTT CTT GCC GAT GGT GGT TGC TCT GGG GGC GCT TAT GAC Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp 305 310 315 320			960
ATC ATA ATA TGT GAT GAG TGC CAT TCA ACT GAC TCG ACT ACA ATC TTG Ile Ile Ile Cys Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu 325 330 335			1008
GGC ATC GGC ACA GTC CTG GAC CAA GCG GAG ACG GCT GGA GCG CGG CTT Gly Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu 340 345 350			1056
GTC GTG CTC GCC ACC GCT ACG CCT CCG GGA TCG GTC ACC GTG CCA CAC Val Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His 355 360 365			1104
CCA AAC ATC GAG GAG GTG GCC CTG TCT AAT ACT GGA GAG ATC CCC TTC Pro Asn Ile Glu Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe 370 375 380			1152
TAT GGC AAA GCC ATC CCC ATT GAA GCC ATC AGG GGG GGA AGG CAT CTC Tyr Gly Lys Ala Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu 385 390 395 400			1200
ATT TTC TGT CAT TCC AAG AAG AAG TGC GAC GAG CTC GCC GCA AAG CTG Ile Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu 405 410 415			1248
TCA GGC CTC GGA ATC AAC GCT GTG GCG TAT TAC CGG GGG CTC GAT GTG Ser Gly Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val 420 425 430			1296

TCC GTC ATA CCA ACT ATC GGA GAC GTC GTT GTC GTG GCA ACA GAC GCT Ser Val Ile Pro Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala 435 440 445	1344
CTG ATG ACG GGC TAT ACG GGC GAC TTT GAC TCA GTG ATC GAC TGT AAC Leu Met Thr Gly Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn 450 455 460	1392
ACA TGT GTC ACC CAG ACA GTC GAC TTC AGC TTG GAT CCC ACC TTC ACC Thr Cys Val Thr Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr 465 470 475 480	1440
ATT GAG ACG ACG ACC GTG CCT CAA GAC GCA GTG TCG CGC TCG CAG CGG Ile Glu Thr Thr Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg 485 490 495	1488
CGG GGT AGG ACT GGC AGG GGT AGG AGA GGC ATC TAC AGG TTT GTG ACT Arg Gly Arg Thr Gly Arg Gly Arg Arg Gly Ile Tyr Arg Phe Val Thr 500 505 510	1536
CCG GGA GAA CGG CCC TCG GGC ATG TTC GAT TCC TCG GTC CTG TGT GAG Pro Gly Glu Arg Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu 515 520 525	1584
TGC TAT GAC GCG GGC TGT GCT TGG TAC GAG CTC ACC CCC GCC GAG ACC Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr 530 535 540	1632
TCG GTT AGG TTG CGG GCC TAC CTG AAC ACA CCA GGG TTG CCC GTT TGC Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys 545 550 555 560	1680
CAG GAC CAC CTG GAG TTC TGG GAG AGT GTC TTC ACA GGC CTC ACC CAT Gln Asp His Leu Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His 565 570 575	1728
ATA GAT GCA CAC TTC TTG TCC CAG ACC AAG CAG GCA GGA GAC AAC TTC Ile Asp Ala His Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe 580 585 590	1776
CCC TAC CTG GTA GCA TAC CAA GCC ACG GTG TGC GCC AGG GCT CAG GCC Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala 595 600 605	1824
CCA CCT CCA TCA TGG GAT CAA ATG TGG AAG TGT CTC ATA CGG CTG AAA Pro Pro Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys 610 615 620	1872
CCT ACG CTG CAC GGG CCA ACA CCC TTG CTG TAC AGG CTG GGA GCC GTC Pro Thr Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val 625 630 635 640	1920
CAA AAT GAG GTC ACC CTC ACC CAC CCC ATA ACC AAA TAC ATC ATG GCA Gln Asn Glu Val Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala 645 650 655	1968
TGC ATG TCG GCT GAC CTG GAG GTC GTC ACT Cys Met Ser Ala Asp Leu Glu Val Val	1998

SUBSTITUTE SHEET (rule 26)

660

665

(2) INFORMATION FOR SEQ ID NO:108:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1998 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:108

ATG GGC AGC AGC CAT CAT CAT CAT CAC AGC AGC GGC CTG GTG CCG	48
Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro	
1 5 10 15	
CGC GGC AGC CAT ATG GGT TCT GTT GTT ATT GTT GGT AGA ATT ATT TTA	96
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu	
20 25 30	
TCT GGT AGT GGT AGT ATC ACG GCC TAC TCC CAA CAG ACG CGG GGC CTA	144
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu	
35 40 45	
CTT GGT TGC ATC AAG ACT AGC CTT ACA GGC CGG GAC AAG AAC CAG GTC	192
Leu Gly Cys Ile Lys Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val	
50 55 60	
GAG GGA GAG GTT CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG	240
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala	
65 70 75 80	
ACC TGC GTC AAC GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA	288
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser	
85 90 95	
AAG ACC TTA GCC GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT	336
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn	
100 105 110	
GTG GAC CAG GAC CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC	384
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser	
115 120 125	
TTG ACA CCA TGC ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA	432
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg	
130 135 140	

CAT GCT GAC GTC ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser 145 150 155 160	480
CTG CTC TCC CCC AGG CCT GTC TCC TAC TTG AAG GGC TCT GCT GGT GGT Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ala Gly Gly 165 170 175	528
CCA CTG CTC TGC CCT TCG GGG CAC GCT GTG GGC ATC TTC CGG GCT GCC Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala 180 185 190	576
GTA TGC ACC CGG GGG GTT GCG AAG GCG GTG GAC TTT GTG CCC GTA GAG Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu 195 200 205	624
TCC ATG GAA ACT ACT ATG CGG TCT CCG GTC TTC ACG GAC AAC TCA TCC Ser Met Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser 210 215 220	672
CCC CCG GCC GTA CCG CAG TCA TTT CAA GTG GCC CAC CTA CAC GCT CCC Pro Pro Ala Val Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro 225 230 235 240	720
ACT GGC AGC GGC AAG AGT ACT AAA GTG CCG GCT GCA TAT GCA GCC CAA Thr Gly Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln 245 250 255	768
GGG TAC AAG GTG CTC GTC CTC AAT CCG TCC GTT GCC GCT ACC TTA GGG Gly Tyr Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly 260 265 270	816
TTT GGG GCG TAT ATG TCT AAG GCA CAC GGT ATT GAC CCC AAC ATC AGA Phe Gly Ala Tyr Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg 275 280 285	864
ACT GGG GTA AGG ACC ATT ACC ACA GGC GCC CCC GTC ACA TAC TCT ACC Thr Gly Val Arg Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr 290 295 300	912
TAT GGC AAG TTT CTT GCC GAT GGT GGT TGC TCT GGG GGC GCT TAT GAC Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp 305 310 315 320	960
ATC ATA ATA TGT GAT GAG TGC CAT TCA ACT GAC TCG ACT ACA ATC TTG Ile Ile Ile Cys Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu 325 330 335	1008
GGC ATC GGC ACA GTC CTG GAC CAA GCG GAG ACG GCT GGA GCG CGG CTT Gly Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu 340 345 350	1056
GTC GTG CTC GCC ACC GCT ACG CCT CCG GGA TCG GTC ACC GTG CCA CAC Val Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His 355 360 365	1104
CCA AAC ATC GAG GAG GTG GCC CTG TCT AAT ACT GGA GAG ATC CCC TTC	1152

SUBSTITUTE SHEET (rule 26)

Pro	Asn	Ile	Glu	Glu	Val	Ala	Leu	Ser	Asn	Thr	Gly	Glu	Ile	Pro	Phe	
370						375					380					
TAT	GGC	AAA	GCC	ATC	CCC	ATT	GAA	GCC	ATC	AGG	GGG	GGA	AGG	CAT	CTC	1200
Tyr	Gly	Lys	Ala	Ile	Pro	Ile	Glu	Ala	Ile	Arg	Gly	Gly	Arg	His	Leu	
385					390				395					400		
ATT	TTC	TGT	CAT	TCC	AAG	AAG	AAG	TGC	GAC	GAG	CTC	GCC	GCA	AAG	CTG	1248
Ile	Phe	Cys	His	Ser	Lys	Lys	Lys	Cys	Asp	Glu	Leu	Ala	Ala	Lys	Leu	
				405				410						415		
TCA	GGC	CTC	GGA	ATC	AAC	GCT	GTG	GCG	TAT	TAC	CGG	GGG	CTC	GAT	GTG	1296
Ser	Gly	Leu	Gly	Ile	Asn	Ala	Val	Ala	Tyr	Tyr	Arg	Gly	Leu	Asp	Val	
			420				425						430			
TCC	GTC	ATA	CCA	ACT	ATC	GGA	GAC	GTC	GTT	GTC	GTG	GCA	ACA	GAC	GCT	1344
Ser	Val	Ile	Pro	Thr	Ile	Gly	Asp	Val	Val	Val	Val	Ala	Thr	Asp	Ala	
		435				440						445				
CTG	ATG	ACG	GGC	TAT	ACG	GGC	GAC	TTT	GAC	TCA	GTG	ATC	GAC	TGT	AAC	1392
Leu	Met	Thr	Gly	Tyr	Thr	Gly	Asp	Phe	Asp	Ser	Val	Ile	Asp	Cys	Asn	
	450					455				460						
ACA	TGT	GTC	ACC	CAG	ACA	GTC	GAC	TTC	AGC	TTG	GAT	CCC	ACC	TTC	ACC	1440
Thr	Cys	Val	Thr	Gln	Thr	Val	Asp	Phe	Ser	Leu	Asp	Pro	Thr	Phe	Thr	
465					470					475				480		
ATT	GAG	ACG	ACG	ACC	GTG	CCT	CAA	GAC	GCA	GTG	TCG	CGC	TCG	CAG	CGG	1488
Ile	Glu	Thr	Thr	Thr	Val	Pro	Gln	Asp	Ala	Val	Ser	Arg	Ser	Gln	Arg	
				485				490						495		
CGG	GGT	AGG	ACT	GGC	AGG	GGT	AGG	AGA	GGC	ATC	TAC	AGG	TTT	GTG	ACT	1536
Arg	Gly	Arg	Thr	Gly	Arg	Gly	Arg	Arg	Gly	Ile	Tyr	Arg	Phe	Val	Thr	
			500					505					510			
CCG	GGA	GAA	CGG	CCC	TCG	GGC	ATG	TTC	GAT	TCC	TCG	GTC	CTG	TGT	GAG	1584
Pro	Gly	Glu	Arg	Pro	Ser	Gly	Met	Phe	Asp	Ser	Ser	Val	Leu	Cys	Glu	
		515					520					525				
TGC	TAT	GAC	GCG	GGC	TGT	GCT	TGG	TAC	GAG	CTC	ACC	CCC	GCC	GAG	ACC	1632
Cys	Tyr	Asp	Ala	Gly	Cys	Ala	Trp	Tyr	Glu	Leu	Thr	Pro	Ala	Glu	Thr	
	530					535					540					
TCG	GTT	AGG	TTG	CGG	GCC	TAC	CTG	AAC	ACA	CCA	GGG	TTG	CCC	GTT	TGC	1680
Ser	Val	Arg	Leu	Arg	Ala	Tyr	Leu	Asn	Thr	Pro	Gly	Leu	Pro	Val	Cys	
545					550				555					560		
CAG	GAC	CAC	CTG	GAG	TTC	TGG	GAG	AGT	GTC	TTC	ACA	GGC	CTC	ACC	CAT	1728
Gln	Asp	His	Leu	Glu	Phe	Trp	Glu	Ser	Val	Phe	Thr	Gly	Leu	Thr	His	
				565				570					575			
ATA	GAT	GCA	CAC	TTC	TTG	TCC	CAG	ACC	AAG	CAG	GCA	GGA	GAC	AAC	TTC	1776
Ile	Asp	Ala	His	Phe	Leu	Ser	Gln	Thr	Lys	Gln	Ala	Gly	Asp	Asn	Phe	
			580				585					590				
CCC	TAC	CTG	GTA	GCA	TAC	CAA	GCC	ACG	GTG	TGC	GCC	AGG	GCT	CAG	GCC	1824
Pro	Tyr	Leu	Val	Ala	Tyr	Gln	Ala	Thr	Val	Cys	Ala	Arg	Ala	Gln	Ala	
		595				600						605				

SUBSTITUTE SHEET (rule 26)

CCA CCT CCA TCA TGG GAT CAA ATG TGG AAG TGT CTC ATA CGG CTG AAA	1872
Pro Pro Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys	
610 615 620	
CCT ACG CTG CAC GGG CCA ACA CCC TTG CTG TAC AGG CTG GGA GCC GTC	1920
Pro Thr Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val	
625 630 635 640	
CAA AAT GAG GTC ACC CTC ACC CAC CCC ATA ACC AAA TAC ATC ATG GCA	1968
Gln Asn Glu Val Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala	
645 650 655	
TGC ATG TCG GCT GAC CTG GAG GTC GTC ACT	1998
Cys Met Ser Ala Asp Leu Glu Val Val	
660 665	

(2) INFORMATION FOR SEQ ID NO:109:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1998 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1997

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1995

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

ATG GGC AGC AGC CAT CAT CAT CAT CAT CAC AGC AGC GGC CTG GTG CCG	48
Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro	
1 5 10 15	
CGC GGC AGC CAT ATG GGT TCT GTT GTT ATT GTT GGT AGA ATT ATT TTA	96
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu	
20 25 30	
TCT GGT AGT GGT AGT ATC ACG GCC TAC TCC CAA CAG ACG CGG GGC CTA	144
Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu	
35 40 45	
CTT GGT TGC AAG AAG ACT AGC CTT ACA GGC CGG GAC AAG AAC CAG GTC	192
Leu Gly Cys Lys Lys Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val	
50 55 60	
GAG GGA GAG GTT CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG	240
Glu Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala	

65	70	75	80	
ACC TGC GTC AAC GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA				288
Thr Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser				
85		90	95	
AAG ACC TTA GCC GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT				336
Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn				
100		105	110	
GTG GAC CAG GAC CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC				384
Val Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser				
115		120	125	
TTG ACA CCA TGC ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA				432
Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg				
130		135	140	
CAT GCT GAC GTC ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC				480
His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser				
145		150	155	160
CTG CTC TCC CCC AGG CCT GTC TCC TAC TTG AAG GGC TCT GCT GGT GGT				528
Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ala Gly Gly				
165		170	175	
CCA CTG CTC TGC CCT TCG GGG CAC GCT GTG GGC ATC TTC CGG GCT GCC				576
Pro Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala				
180		185	190	
GTA TGC ACC CGG GGG GTT GCG AAG GCG GTG GAC TTT GTG CCC GTA GAG				624
Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu				
195		200	205	
TCC ATG GAA ACT ACT ATG CGG TCT CCG GTC TTC ACG GAC AAC TCA TCC				672
Ser Met Glu Thr Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser				
210		215	220	
CCC CCG GCC GTA CCG CAG TCA TTT CAA GTG GCC CAC CTA CAC GCT CCC				720
Pro Pro Ala Val Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro				
225		230	235	240
ACT GGC AGC GGC AAG AGT ACT AAA GTG CCG GCT GCA TAT GCA GCC CAA				768
Thr Gly Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln				
245		250	255	
GGG TAC AAG GTG CTC GTC CTC AAT CCG TCC GTT GCC GCT ACC TTA GGG				816
Gly Tyr Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly				
260		265	270	
TTT GGG GCG TAT ATG TCT AAG GCA CAC GGT ATT GAC CCC AAC ATC AGA				864
Phe Gly Ala Tyr Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg				
275		280	285	
ACT GGG GTA AGG ACC ATT ACC ACA GGC GCC CCC GTC ACA TAC TCT ACC				912
Thr Gly Val Arg Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr				
290		295	300	

TAT GGC AAG TTT CTT GCC GAT GGT GGT TGC TCT GGG GGC GCT TAT GAC Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp 305 310 315 320	960
ATC ATA ATA TGT GAT GAG TGC CAT TCA ACT GAC TCG ACT ACA ATC TTG Ile Ile Ile Cys Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu 325 330 335	1008
GGC ATC GGC ACA GTC CTG GAC CAA GCG GAG ACG GCT GGA GCG CGG CTT Gly Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu 340 345 350	1056
GTC GTG CTC GCC ACC GCT ACG CCT CCG GGA TCG GTC ACC GTG CCA CAC Val Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His 355 360 365	1104
CCA AAC ATC GAG GAG GTG GCC CTG TCT AAT ACT GGA GAG ATC CCC TTC Pro Asn Ile Glu Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe 370 375 380	1152
TAT GGC AAA GCC ATC CCC ATT GAA GCC ATC AGG GGG GGA AGG CAT CTC Tyr Gly Lys Ala Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu 385 390 395 400	1200
ATT TTC TGT CAT TCC AAG AAG AAG TGC GAC GAG CTC GCC GCA AAG CTG Ile Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu 405 410 415	1248
TCA GGC CTC GGA ATC AAC GCT GTG GCG TAT TAC CGG GGG CTC GAT GTG Ser Gly Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val 420 425 430	1296
TCC GTC ATA CCA ACT ATC GGA GAC GTC GTT GTC GTG GCA ACA GAC GCT Ser Val Ile Pro Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala 435 440 445	1344
CTG ATG ACG GGC TAT ACG GGC GAC TTT GAC TCA GTG ATC GAC TGT AAC Leu Met Thr Gly Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn 450 455 460	1392
ACA TGT GTC ACC CAG ACA GTC GAC TTC AGC TTG GAT CCC ACC TTC ACC Thr Cys Val Thr Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr 465 470 475 480	1440
ATT GAG ACG ACG ACC GTG CCT CAA GAC GCA GTG TCG CGC TCG CAG CGG Ile Glu Thr Thr Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg 485 490 495	1488
CGG GGT AGG ACT GGC AGG GGT AGG AGA GGC ATC TAC AGG TTT GTG ACT Arg Gly Arg Thr Gly Arg Gly Arg Arg Gly Ile Tyr Arg Phe Val Thr 500 505 510	1536
CCG GGA GAA CGG CCC TCG GGC ATG TTC GAT TCC TCG GTC CTG TGT GAG Pro Gly Glu Arg Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu 515 520 525	1584
TGC TAT GAC GCG GGC TGT GCT TGG TAC GAG CTC ACC CCC GCC GAG ACC Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr	1632

530	535	540	
TCG GTT AGG TTG CGG GCC TAC CTG AAC ACA CCA GGG TTG CCC GTT TGC			1680
Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys			
545	550	555	560
CAG GAC CAC CTG GAG TTC TGG GAG AGT GTC TTC ACA GGC CTC ACC CAT			1728
Gln Asp His Leu Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His			
565	570		575
ATA GAT GCA CAC TTC TTG TCC CAG ACC AAG CAG GCA GGA GAC AAC TTC			1776
Ile Asp Ala His Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe			
580	585		590
CCC TAC CTG GTA GCA TAC CAA GCC ACG GTG TGC GCC AGG GCT CAG GCC			1824
Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala			
595	600		605
CCA CCT CCA TCA TGG GAT CAA ATG TGG AAG TGT CTC ATA CGG CTG AAA			1872
Pro Pro Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys			
610	615		620
CCT ACG CTG CAC GGG CCA ACA CCC TTG CTG TAC AGG CTG GGA GCC GTC			1920
Pro Thr Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val			
625	630	635	640
CAA AAT GAG GTC ACC CTC ACC CAC CCC ATA ACC AAA TAC ATC ATG GCA			1968
Gln Asn Glu Val Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala			
645	650		655
TGC ATG TCG GCT GAC CTG GAG GTC GTC ACT			1998
Cys Met Ser Ala Asp Leu Glu Val Val			
660	665		

(2) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2016 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..2013

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

ATG GGC AGC AGC CAT CAT CAT CAT CAT CAC AGC AGC GGC CTG GTG CCG	48
Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro	
1 5 10 15	

CGC GGC AGC CAT ATG GCT TAC TCT CTG ACT ACG GGT TCT GTT GTT ATT	96
Arg Gly Ser His Met Ala Tyr Ser Leu Thr Thr Gly Ser Val Val Ile	
20 25 30	
GTT GGT AGA ATT ATT TTA TCT GGT AGT GGT AGT ATC ACG GCC TAC TCC	144
Val Gly Arg Ile Ile Leu Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser	
35 40 45	
CAA CAG ACG CGG GGC CTA CTT GGT TGC ATC ATC ACT AGC CTT ACA GGC	192
Gln Gln Thr Arg Gly Leu Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly	
50 55 60	
CGG GAC AAG AAC CAG GTC GAG GGA GAG GTT CAG GTG GTT TCC ACC GCA	240
Arg Asp Lys Asn Gln Val Glu Gly Glu Val Gln Val Val Ser Thr Ala	
65 70 75 80	
ACA CAA TCC TTC CTG GCG ACC TGC GTC AAC GGC GTG TGT TGG ACC GTT	288
Thr Gln Ser Phe Leu Ala Thr Cys Val Asn Gly Val Cys Trp Thr Val	
85 90 95	
TAC CAT GGT GCT GGC TCA AAG ACC TTA GCC GGC CCA AAG GGG CCA ATC	336
Tyr His Gly Ala Gly Ser Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile	
100 105 110	
ACC CAG ATG TAC ACT AAT GTG GAC CAG GAC CTC GTC GGC TGG CAG GCG	384
Thr Gln Met Tyr Thr Asn Val Asp Gln Asp Leu Val Gly Trp Gln Ala	
115 120 125	
CCC CCC GGG GCG CGT TCC TTG ACA CCA TGC ACC TGT GGC AGC TCA GAC	432
Pro Pro Gly Ala Arg Ser Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp	
130 135 140	
CTT TAC TTG GTC ACG AGA CAT GCT GAC GTC ATT CCG GTG CGC CGG CGG	480
Leu Tyr Leu Val Thr Arg His Ala Asp Val Ile Pro Val Arg Arg Arg	
145 150 155 160	
GGC GAC AGT AGG GGG AGC CTG CTC TCC CCC AGG CCT GTC TCC TAC TTG	528
Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu	
165 170 175	
AAG GGC TCT TCG GGT GGT CCA CTG CTC TGC CCT TCG GGG CAC GCT GTG	576
Lys Gly Ser Ser Gly Gly Pro Leu Leu Cys Pro Ser Gly His Ala Val	
180 185 190	
GGC ATC TTC CGG GCT GCC GTA TGC ACC CGG GGG GTT GCG AAG GCG GTG	624
Gly Ile Phe Arg Ala Ala Val Cys Thr Arg Gly Val Ala Lys Ala Val	
195 200 205	
GAC TTT GTG CCC GTA GAG TCC ATG GAA ACT ACT ATG CGG TCT CCG GTC	672
Asp Phe Val Pro Val Glu Ser Met Glu Thr Thr Met Arg Ser Pro Val	
210 215 220	
TTC ACG GAC AAC TCA TCC CCC CCG GCC GTA CCG CAG TCA TTT CAA GTG	720
Phe Thr Asp Asn Ser Ser Pro Pro Ala Val Pro Gln Ser Phe Gln Val	
225 230 235 240	
GCC CAC CTA CAC GCT CCC ACT GGC AGC GGC AAG AGT ACT AAA GTG CCG	768

Ala	His	Leu	His	Ala	Pro	Thr	Gly	Ser	Gly	Lys	Ser	Thr	Lys	Val	Pro		
				245					250					255			
GCT	GCA	TAT	GCA	GCC	CAA	GGG	TAC	AAG	GTG	CTC	GTC	CTC	AAT	CCG	TCC	816	
Ala	Ala	Tyr	Ala	Ala	Gln	Gly	Tyr	Lys	Val	Leu	Val	Leu	Asn	Pro	Ser		
			260					265					270				
GTT	GCC	GCT	ACC	TTA	GGG	TTT	GGG	GCG	TAT	ATG	TCT	AAG	GCA	CAC	GGT	864	
Val	Ala	Ala	Thr	Leu	Gly	Phe	Gly	Ala	Tyr	Met	Ser	Lys	Ala	His	Gly		
			275				280					285					
ATT	GAC	CCC	AAC	ATC	AGA	ACT	GGG	GTA	AGG	ACC	ATT	ACC	ACA	GGC	GCC	912	
Ile	Asp	Pro	Asn	Ile	Arg	Thr	Gly	Val	Arg	Thr	Ile	Thr	Thr	Gly	Ala		
	290					295					300						
CCC	GTC	ACA	TAC	TCT	ACC	TAT	GGC	AAG	TTT	CTT	GCC	GAT	GGT	GGT	TGC	960	
Pro	Val	Thr	Tyr	Ser	Thr	Tyr	Gly	Lys	Phe	Leu	Ala	Asp	Gly	Gly	Cys		
305					310					315					320		
TCT	GGG	GGC	GCT	TAT	GAC	ATC	ATA	ATA	TGT	GAT	GAG	TGC	CAT	TCA	ACT	1008	
Ser	Gly	Gly	Ala	Tyr	Asp	Ile	Ile	Ile	Cys	Asp	Glu	Cys	His	Ser	Thr		
				325					330					335			
GAC	TCG	ACT	ACA	ATC	TTG	GGC	ATC	GGC	ACA	GTC	CTG	GAC	CAA	GCG	GAG	1056	
Asp	Ser	Thr	Thr	Ile	Leu	Gly	Ile	Gly	Thr	Val	Leu	Asp	Gln	Ala	Glu		
			340					345					350				
ACG	GCT	GGA	GCG	CGG	CTT	GTC	GTG	CTC	GCC	ACC	GCT	ACG	CCT	CCG	GGA	1104	
Thr	Ala	Gly	Ala	Arg	Leu	Val	Val	Leu	Ala	Thr	Ala	Thr	Pro	Pro	Gly		
		355					360					365					
TCG	GTC	ACC	GTG	CCA	CAC	CCA	AAC	ATC	GAG	GAG	GTG	GCC	CTG	TCT	AAT	1152	
Ser	Val	Thr	Val	Pro	His	Pro	Asn	Ile	Glu	Glu	Val	Ala	Leu	Ser	Asn		
	370					375					380						
ACT	GGA	GAG	ATC	CCC	TTC	TAT	GGC	AAA	GCC	ATC	CCC	ATT	GAA	GCC	ATC	1200	
Thr	Gly	Glu	Ile	Pro	Phe	Tyr	Gly	Lys	Ala	Ile	Pro	Ile	Glu	Ala	Ile		
385					390				395					400			
AGG	GGG	GGA	AGG	CAT	CTC	ATT	TTC	TGT	CAT	TCC	AAG	AAG	AAG	TGC	GAC	1248	
Arg	Gly	Gly	Arg	His	Leu	Ile	Phe	Cys	His	Ser	Lys	Lys	Lys	Cys	Asp		
				405				410						415			
GAG	CTC	GCC	GCA	AAG	CTG	TCA	GGC	CTC	GGA	ATC	AAC	GCT	GTG	GCG	TAT	1296	
Glu	Leu	Ala	Ala	Lys	Leu	Ser	Gly	Leu	Gly	Ile	Asn	Ala	Val	Ala	Tyr		
			420					425					430				
TAC	CGG	GGG	CTC	GAT	GTG	TCC	GTC	ATA	CCA	ACT	ATC	GGA	GAC	GTC	GTT	1344	
Tyr	Arg	Gly	Leu	Asp	Val	Ser	Val	Ile	Pro	Thr	Ile	Gly	Asp	Val	Val		
			435				440					445					
GTC	GTG	GCA	ACA	GAC	GCT	CTG	ATG	ACG	GGC	TAT	ACG	GGC	GAC	TTT	GAC	1392	
Val	Val	Ala	Thr	Asp	Ala	Leu	Met	Thr	Gly	Tyr	Thr	Gly	Asp	Phe	Asp		
	450					455					460						
TCA	GTG	ATC	GAC	TGT	AAC	ACA	TGT	GTC	ACC	CAG	ACA	GTC	GAC	TTC	AGC	1440	
Ser	Val	Ile	Asp	Cys	Asn	Thr	Cys	Val	Thr	Gln	Thr	Val	Asp	Phe	Ser		
465					470				475					480			

SUBSTITUTE SHEET (rule 26)

TTG GAT CCC ACC TTC ACC ATT GAG ACG ACG ACC GTG CCT CAA GAC GCA	1488
Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr Thr Val Pro Gln Asp Ala	
485 490 495	
GTG TCG CGC TCG CAG CGG CGG GGT AGG ACT GGC AGG GGT AGG AGA GGC	1536
Val Ser Arg Ser Gln Arg Arg Gly Arg Thr Gly Arg Gly Arg Gly	
500 505 510	
ATC TAC AGG TTT GTG ACT CCG GGA GAA CGG CCC TCG GGC ATG TTC GAT	1584
Ile Tyr Arg Phe Val Thr Pro Gly Glu Arg Pro Ser Gly Met Phe Asp	
515 520 525	
TCC TCG GTC CTG TGT GAG TGC TAT GAC GCG GGC TGT GCT TGG TAC GAG	1632
Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu	
530 535 540	
CTC ACC CCC GCC GAG ACC TCG GTT AGG TTG CGG GCC TAC CTG AAC ACA	1680
Leu Thr Pro Ala Glu Thr Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr	
545 550 555 560	
CCA GGG TTG CCC GTT TGC CAG GAC CAC CTG GAG TTC TGG GAG AGT GTC	1728
Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Ser Val	
565 570 575	
TTC ACA GGC CTC ACC CAT ATA GAT GCA CAC TTC TTG TCC CAG ACC AAG	1776
Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr Lys	
580 585 590	
CAG GCA GGA GAC AAC TTC CCC TAC CTG GTA GCA TAC CAA GCC ACG GTG	1824
Gln Ala Gly Asp Asn Phe Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val	
595 600 605	
TGC GCC AGG GCT CAG GCC CCA CCT CCA TCA TGG GAT CAA ATG TGG AAG	1872
Cys Ala Arg Ala Gln Ala Pro Pro Ser Trp Asp Gln Met Trp Lys	
610 615 620	
TGT CTC ATA CGG CTG AAA CCT ACG CTG CAC GGG CCA ACA CCC TTG CTG	1920
Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu Leu	
625 630 635 640	
TAC AGG CTG GGA GCC GTC CAA AAT GAG GTC ACC CTC ACC CAC CCC ATA	1968
Tyr Arg Leu Gly Ala Val Gln Asn Glu Val Thr Leu Thr His Pro Ile	
645 650 655	
ACC AAA TAC ATC ATG GCA TGC ATG TCG GCT GAC CTG GAG GTC GTC	2013
Thr Lys Tyr Ile Met Ala Cys Met Ser Ala Asp Leu Glu Val Val	
660 665 670	
ACT	2016

(2) INFORMATION FOR SEQ ID NO:111:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2016 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..2013

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

ATG GGC AGC AGC CAT CAT CAT CAT CAT CAC AGC AGC GGC CTG GTG CCG	48
Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro	
1 5 10 15	
CGC GGC AGC CAT ATG GCT TAC TCT CTG ACT ACG GGT TCT GTT GTT ATT	96
Arg Gly Ser His Met Ala Tyr Ser Leu Thr Thr Gly Ser Val Val Ile	
20 25 30	
GTT GGT AGA ATT ATT TTA TCT GGT AGT GGT AGT ATC ACG GCC TAC TCC	144
Val Gly Arg Ile Ile Leu Ser Gly Ser Gly Ser Ile Thr Ala Tyr Ser	
35 40 45	
CAA CAG ACG CGG GGC CTA CTT GGT TGC ATC ATC ACT AGC CTT ACA GGC	192
Gln Gln Thr Arg Gly Leu Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly	
50 55 60	
CGG GAC AAG AAC CAG GTC GAG GGA GAG GTT CAG GTG GTT TCC ACC GCA	240
Arg Asp Lys Asn Gln Val Glu Gly Glu Val Gln Val Val Ser Thr Ala	
65 70 75 80	
ACA CAA TCC TTC CTG GCG ACC TGC GTC AAC GGC GTG TGT TGG ACC GTT	288
Thr Gln Ser Phe Leu Ala Thr Cys Val Asn Gly Val Cys Trp Thr Val	
85 90 95	
TAC CAT GGT GCT GGC TCA AAG ACC TTA GCC GGC CCA AAG GGG CCA ATC	336
Tyr His Gly Ala Gly Ser Lys Thr Leu Ala Gly Pro Lys Gly Pro Ile	
100 105 110	
ACC CAG ATG TAC ACT AAT GTG GAC CAG GAC CTC GTC GGC TGG CAG GCG	384
Thr Gln Met Tyr Thr Asn Val Asp Gln Asp Leu Val Gly Trp Gln Ala	
115 120 125	
CCC CCC GGG GCG CGT TCC TTG ACA CCA TGC ACC TGT GGC AGC TCA GAC	432
Pro Pro Gly Ala Arg Ser Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp	
130 135 140	
CTT TAC TTG GTC ACG AGA CAT GCT GAC GTC ATT CCG GTG CGC CGG CGG	480
Leu Tyr Leu Val Thr Arg His Ala Asp Val Ile Pro Val Arg Arg Arg	
145 150 155 160	
GGC GAC AGT AGG GGG AGC CTG CTC TCC CCC AGG CCT GTC TCC TAC TTG	528
Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu	
165 170 175	
AAG GGC TCT GCT GGT GGT CCA CTG CTC TGC CCT TCG GGG CAC GCT GTG	576

SUBSTITUTE SHEET (rule 26)

Lys Gly Ser Ala Gly Gly Pro Leu Leu Cys Pro Ser Gly His Ala Val	
180 185 190	
GGC ATC TTC CGG GCT GCC GTA TGC ACC CGG GGG GTT GCG AAG GCG GTG	624
Gly Ile Phe Arg Ala Ala Val Cys Thr Arg Gly Val Ala Lys Ala Val	
195 200 205	
GAC TTT GTG CCC GTA GAG TCC ATG GAA ACT ACT ATG CGG TCT CCG GTC	672
Asp Phe Val Pro Val Glu Ser Met Glu Thr Thr Met Arg Ser Pro Val	
210 215 220	
TTC ACG GAC AAC TCA TCC CCC CCG GCC GTA CCG CAG TCA TTT CAA GTG	720
Phe Thr Asp Asn Ser Ser Pro Pro Ala Val Pro Gln Ser Phe Gln Val	
225 230 235 240	
GCC CAC CTA CAC GCT CCC ACT GGC AGC GGC AAG AGT ACT AAA GTG CCG	768
Ala His Leu His Ala Pro Thr Gly Ser Gly Lys Ser Thr Lys Val Pro	
245 250 255	
GCT GCA TAT GCA GCC CAA GGG TAC AAG GTG CTC GTC CTC AAT CCG TCC	816
Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val Leu Val Leu Asn Pro Ser	
260 265 270	
GTT GCC GCT ACC TTA GGG TTT GGG GCG TAT ATG TCT AAG GCA CAC GGT	864
Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His Gly	
275 280 285	
ATT GAC CCC AAC ATC AGA ACT GGG GTA AGG ACC ATT ACC ACA GGC GCC	912
Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly Ala	
290 295 300	
CCC GTC ACA TAC TCT ACC TAT GGC AAG TTT CTT GCC GAT GGT GGT TGC	960
Pro Val Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys	
305 310 315 320	
TCT GGG GGC GCT TAT GAC ATC ATA ATA TGT GAT GAG TGC CAT TCA ACT	1008
Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser Thr	
325 330 335	
GAC TCG ACT ACA ATC TTG GGC ATC GGC ACA GTC CTG GAC CAA GCG GAG	1056
Asp Ser Thr Thr Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala Glu	
340 345 350	
ACG GCT GGA GCG CGG CTT GTC GTG CTC GCC ACC GCT ACG CCT CCG GGA	1104
Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro Gly	
355 360 365	
TCG GTC ACC GTG CCA CAC CCA AAC ATC GAG GAG GTG GCC CTG TCT AAT	1152
Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser Asn	
370 375 380	
ACT GGA GAG ATC CCC TTC TAT GGC AAA GCC ATC CCC ATT GAA GCC ATC	1200
Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Ile Glu Ala Ile	
385 390 395 400	
AGG GGG GGA AGG CAT CTC ATT TTC TGT CAT TCC AAG AAG AAG TGC GAC	1248
Arg Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys Asp	
405 410 415	

SUBSTITUTE SHEET (rule 26)

GAG	CTC	GCC	GCA	AAG	CTG	TCA	GGC	CTC	GGA	ATC	AAC	GCT	GTG	GCG	TAT	1296
Glu	Leu	Ala	Ala	Lys	Leu	Ser	Gly	Leu	Gly	Ile	Asn	Ala	Val	Ala	Tyr	
			420					425					430			
TAC	CGG	GGG	CTC	GAT	GTG	TCC	GTC	ATA	CCA	ACT	ATC	GGA	GAC	GTC	GTT	1344
Tyr	Arg	Gly	Leu	Asp	Val	Ser	Val	Ile	Pro	Thr	Ile	Gly	Asp	Val	Val	
		435					440					445				
GTC	GTG	GCA	ACA	GAC	GCT	CTG	ATG	ACG	GGC	TAT	ACG	GGC	GAC	TTT	GAC	1392
Val	Val	Ala	Thr	Asp	Ala	Leu	Met	Thr	Gly	Tyr	Thr	Gly	Asp	Phe	Asp	
		450					455				460					
TCA	GTG	ATC	GAC	TGT	AAC	ACA	TGT	GTC	ACC	CAG	ACA	GTC	GAC	TTC	AGC	1440
Ser	Val	Ile	Asp	Cys	Asn	Thr	Cys	Val	Thr	Gln	Thr	Val	Asp	Phe	Ser	
465					470					475					480	
TTG	GAT	CCC	ACC	TTC	ACC	ATT	GAG	ACG	ACG	ACC	GTG	CCT	CAA	GAC	GCA	1488
Leu	Asp	Pro	Thr	Phe	Thr	Ile	Glu	Thr	Thr	Thr	Val	Pro	Gln	Asp	Ala	
				485					490					495		
GTG	TCG	CGC	TCG	CAG	CGG	CGG	GGT	AGG	ACT	GGC	AGG	GGT	AGG	AGA	GGC	1536
Val	Ser	Arg	Ser	Gln	Arg	Arg	Gly	Arg	Thr	Gly	Arg	Gly	Arg	Arg	Gly	
			500					505					510			
ATC	TAC	AGG	TTT	GTG	ACT	CCG	GGA	GAA	CGG	CCC	TCG	GGC	ATG	TTC	GAT	1584
Ile	Tyr	Arg	Phe	Val	Thr	Pro	Gly	Glu	Arg	Pro	Ser	Gly	Met	Phe	Asp	
		515					520					525				
TCC	TCG	GTC	CTG	TGT	GAG	TGC	TAT	GAC	GCG	GGC	TGT	GCT	TGG	TAC	GAG	1632
Ser	Ser	Val	Leu	Cys	Glu	Cys	Tyr	Asp	Ala	Gly	Cys	Ala	Trp	Tyr	Glu	
		530					535					540				
CTC	ACC	CCC	GCC	GAG	ACC	TCG	GTT	AGG	TTG	CGG	GCC	TAC	CTG	AAC	ACA	1680
Leu	Thr	Pro	Ala	Glu	Thr	Ser	Val	Arg	Leu	Arg	Ala	Tyr	Leu	Asn	Thr	
545					550					555					560	
CCA	GGG	TTG	CCC	GTT	TGC	CAG	GAC	CAC	CTG	GAG	TTC	TGG	GAG	AGT	GTC	1728
Pro	Gly	Leu	Pro	Val	Cys	Gln	Asp	His	Leu	Glu	Phe	Trp	Glu	Ser	Val	
				565					570				575			
TTC	ACA	GGC	CTC	ACC	CAT	ATA	GAT	GCA	CAC	TTC	TTG	TCC	CAG	ACC	AAG	1776
Phe	Thr	Gly	Leu	Thr	His	Ile	Asp	Ala	His	Phe	Leu	Ser	Gln	Thr	Lys	
			580					585					590			
CAG	GCA	GGA	GAC	AAC	TTC	CCC	TAC	CTG	GTA	GCA	TAC	CAA	GCC	ACG	GTG	1824
Gln	Ala	Gly	Asp	Asn	Phe	Pro	Tyr	Leu	Val	Ala	Tyr	Gln	Ala	Thr	Val	
		595					600					605				
TGC	GCC	AGG	GCT	CAG	GCC	CCA	CCT	CCA	TCA	TGG	GAT	CAA	ATG	TGG	AAG	1872
Cys	Ala	Arg	Ala	Gln	Ala	Pro	Pro	Pro	Ser	Trp	Asp	Gln	Met	Trp	Lys	
		610					615				620					
TGT	CTC	ATA	CGG	CTG	AAA	CCT	ACG	CTG	CAC	GGG	CCA	ACA	CCC	TTG	CTG	1920
Cys	Leu	Ile	Arg	Leu	Lys	Pro	Thr	Leu	His	Gly	Pro	Thr	Pro	Leu	Leu	
625					630					635				640		
TAC	AGG	CTG	GGA	GCC	GTC	CAA	AAT	GAG	GTC	ACC	CTC	ACC	CAC	CCC	ATA	1968

SUBSTITUTE SHEET (rule 26)

Tyr	Arg	Leu	Gly	Ala	Val	Gln	Asn	Glu	Val	Thr	Leu	Thr	His	Pro	Ile		
				645					650					655			
ACC	AAA	TAC	ATC	ATG	GCA	TGC	ATG	TCG	GCT	GAC	CTG	GAG	GTC	GTC		2013	
Thr	Lys	Tyr	Ile	Met	Ala	Cys	Met	Ser	Ala	Asp	Leu	Glu	Val	Val			
				660				665					670				
ACT																2016	

(2) INFORMATION FOR SEQ ID NO:112:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 648 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..648

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

ATG	GGC	AGC	AGC	CAT	CAT	CAT	CAT	CAT	CAC	AGC	AGC	GGC	CTG	GTG	CCG	48
Met	Gly	Ser	Ser	His	His	His	His	His	His	Ser	Ser	Gly	Leu	Val	Pro	
1				5					10					15		
CGC	GGC	AGC	CAT	ATG	GGT	TCT	GTT	GTT	ATT	GTT	GGT	AGA	ATT	ATT	TTA	96
Arg	Gly	Ser	His	Met	Gly	Ser	Val	Val	Ile	Val	Gly	Arg	Ile	Ile	Leu	
			20				25					30				
TCT	CCT	GCT	GGT	ATC	ACG	GCC	TAC	TCC	CAA	CAG	ACG	CGG	GGC	CTA	CTT	144
Ser	Pro	Ala	Gly	Ile	Thr	Ala	Tyr	Ser	Gln	Gln	Thr	Arg	Gly	Leu	Leu	
		35				40					45					
GGT	TGC	ATC	ATC	ACT	AGC	CTT	ACA	GGC	CGG	GAC	AAG	AAC	CAG	GTC	GAG	192
Gly	Cys	Ile	Ile	Thr	Ser	Leu	Thr	Gly	Arg	Asp	Lys	Asn	Gln	Val	Glu	
	50					55				60						
GGA	GAG	GTT	CAG	GTG	GTT	TCC	ACC	GCA	ACA	CAA	TCC	TTC	CTG	GCG	ACC	240
Gly	Glu	Val	Gln	Val	Val	Ser	Thr	Ala	Thr	Gln	Ser	Phe	Leu	Ala	Thr	
	65				70				75					80		
TGC	GTC	AAC	GGC	GTG	TGT	TGG	ACC	GTT	TAC	CAT	GGT	GCT	GGC	TCA	AAG	288
Cys	Val	Asn	Gly	Val	Cys	Trp	Thr	Val	Tyr	His	Gly	Ala	Gly	Ser	Lys	
			85				90						95			
ACC	TTA	GCC	GGC	CCA	AAG	GGG	CCA	ATC	ACC	CAG	ATG	TAC	ACT	AAT	GTG	336
Thr	Leu	Ala	Gly	Pro	Lys	Gly	Pro	Ile	Thr	Gln	Met	Tyr	Thr	Asn	Val	
			100				105						110			
GAC	CAG	GAC	CTC	GTC	GGC	TGG	CAG	GCG	CCC	CCC	GGG	GCG	CGT	TCC	TTG	384

Asp	Gln	Asp	Leu	Val	Gly	Trp	Gln	Ala	Pro	Pro	Gly	Ala	Arg	Ser	Leu		
	115						120					125					
ACA	CCA	TGC	ACC	TGT	GGC	AGC	TCA	GAC	CTT	TAC	TTG	GTC	ACG	AGA	CAT	432	
Thr	Pro	Cys	Thr	Cys	Gly	Ser	Ser	Asp	Leu	Tyr	Leu	Val	Thr	Arg	His		
	130					135					140						
GCT	GAC	GTC	ATT	CCG	GTG	CGC	CGG	CGG	GGC	GAC	AGT	AGG	GGG	AGC	CTG	480	
Ala	Asp	Val	Ile	Pro	Val	Arg	Arg	Arg	Gly	Asp	Ser	Arg	Gly	Ser	Leu		
145					150					155					160		
CTC	TCC	CCC	AGG	CCT	GTC	TCC	TAC	TTG	AAG	GGC	TCT	TCG	GGT	GGT	CCA	528	
Leu	Ser	Pro	Arg	Pro	Val	Ser	Tyr	Leu	Lys	Gly	Ser	Ser	Gly	Gly	Pro		
				165					170					175			
CTG	CTC	TGC	CCT	TCG	GGG	CAC	GCT	GTG	GGC	ATC	TTC	CGG	GCT	GCC	GTA	576	
Leu	Leu	Cys	Pro	Ser	Gly	His	Ala	Val	Gly	Ile	Phe	Arg	Ala	Ala	Val		
			180					185					190				
TGC	ACC	CGG	GGG	GTT	GCG	AAG	GCG	GTG	GAC	TTT	GTG	CCC	GTA	GAG	TCC	624	
Cys	Thr	Arg	Gly	Val	Ala	Lys	Ala	Val	Asp	Phe	Val	Pro	Val	Glu	Ser		
	195					200						205					
ATG	GAA	ACT	ACT	ATG	CGG	TCT	TGA									648	
Met	Glu	Thr	Thr	Met	Arg	Ser	*										
	210					215											

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 648 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..640

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:113

ATG	GGC	AGC	AGC	CAT	CAT	CAT	CAT	CAT	CAC	AGC	AGC	GGC	CTG	GTG	CCG	48	
Met	Gly	Ser	Ser	His	His	His	His	His	His	Ser	Ser	Gly	Leu	Val	Pro		
1				5					10					15			
CGC	GGC	AGC	CAT	ATG	GGT	TCT	GTT	GTT	ATT	GTT	GGT	AGA	ATT	ATT	TTA	96	
Arg	Gly	Ser	His	Met	Gly	Ser	Val	Val	Ile	Val	Gly	Arg	Ile	Ile	Leu		
			20				25					30					
TCT	CCT	GCT	GGT	ATC	ACG	GCC	TAC	TCC	CAA	CAG	ACG	CGG	GGC	CTA	CTT	144	
Ser	Pro	Ala	Gly	Ile	Thr	Ala	Tyr	Ser	Gln	Gln	Thr	Arg	Gly	Leu	Leu		
			35				40					45					

GGT TGC AAG ATC ACT AGC CTT ACA GGC CGG GAC AAG AAC CAG GTC GAG Gly Cys Lys Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val Glu 50 55 60	192
GGA GAG GTT CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG ACC Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala Thr 65 70 75 80	240
TGC GTC AAC GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA AAG Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser Lys 85 90 95	288
ACC TTA GCC GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT GTG Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn Val 100 105 110	336
GAC CAG GAC CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC TTG Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser Leu 115 120 125	384
ACA CCA TGC ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA CAT Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His 130 135 140	432
GCT GAC GTC ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC CTG Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser Leu 145 150 155 160	480
CTC TCC CCC AGG CCT GTC TCC TAC TTG AAG GGC TCT TCG GGT GGT CCA Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly Pro 165 170 175	528
CTG CTC TGC CCT TCG GGG CAC GCT GTG GGC ATC TTC CGG GCT GCC GTA Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala Val 180 185 190	576
TGC ACC CGG GGG GTT GCG AAG GCG GTG GAC TTT GTG CCC GTA GAG TCC Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu Ser 195 200 205	624
ATG GAA ACT ACT ATG C GGTCTTGA Met Glu Thr Thr Met 210	648

(2) INFORMATION FOR SEQ ID NO:114:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 498 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 1..498

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

ATG ATC ACT AGC CTT ACA GGC CGG GAC AAG AAC CAG GTC GAG GGA GAG	48
Met Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val Glu Gly Glu	
1 5 10 15	
GTT CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG ACC TGC GTC	96
Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala Thr Cys Val	
20 25 30	
AAC GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA AAG ACC TTA	144
Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser Lys Thr Leu	
35 40 45	
GCC GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT GTG GAC CAG	192
Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn Val Asp Gln	
50 55 60	
GAC CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC TTG ACA CCA	240
Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser Leu Thr Pro	
65 70 75 80	
TGC ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA CAT GCT GAC	288
Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His Ala Asp	
85 90 95	
GTC ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC CTG CTC TCC	336
Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser Leu Leu Ser	
100 105 110	
CCC AGG CCT GTC TCC TAC TTG AAG GGC TCT TCG GGT GGT CCA CTG CTC	384
Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly Pro Leu Leu	
115 120 125	
TGC CCT TCG GGG CAC GCT GTG GGC ATC TTC CGG GCT GCC GTA TGC ACC	432
Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala Val Cys Thr	
130 135 140	
CGG GGG GTT GCG AAG GCG GTG GAC TTT GTG CCC GTA GAG TCC ATG GAA	480
Arg Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu Ser Met Glu	
145 150 155 160	
ACT ACT ATG CGG TCT TGA	498
Thr Thr Met Arg Ser *	
165	

(2) INFORMATION FOR SEQ ID NO:115:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 648 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..648

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

ATG GGC AGC AGC CAT CAT CAT CAT CAT CAC AGC AGC GGC CTG GTG CCG	48
Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro	
1 5 10 15	
CGC GGC AGC CAT ATG GGT TCT GTT GTT ATT GTT GGT AGA ATT ATT TTA	96
Arg Gly Ser His Met Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu	
20 25 30	
TCT GGT GGT TCT ATC ACG GCC TAC TCC CAA CAG ACG CGG GGC CTA CTT	144
Ser Gly Gly Ser Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu Leu	
35 40 45	
GGT TGC AAG ATC ACT AGC CTT ACA GGC CGG GAC AAG AAC CAG GTC GAG	192
Gly Cys Lys Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val Glu	
50 55 60	
GGA GAG GTT CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG ACC	240
Gly Glu Val Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala Thr	
65 70 75 80	
TGC GTC AAC GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA AAG	288
Cys Val Asn Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser Lys	
85 90 95	
ACC TTA GCC GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT GTG	336
Thr Leu Ala Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn Val	
100 105 110	
GAC CAG GAC CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC TTG	384
Asp Gln Asp Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser Leu	
115 120 125	
ACA CCA TGC ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA CAT	432
Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His	
130 135 140	
GCT GAC GTC ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC CTG	480
Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser Leu	
145 150 155 160	
CTC TCC CCC AGG CCT GTC TCC TAC TTG AAG GGC TCT TCG GGT GGT CCA	528
Leu Ser Pro Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly Pro	
165 170 175	
CTG CTC TGC CCT TCG GGG CAC GCT GTG GGC ATC TTC CGG GCT GCC GTA	576
Leu Leu Cys Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala Val	

[illegible]

(2) INFORMATION FOR SEQ ID NO:116:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2007 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
(B) LOCATION: 1..2004

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

ATG	CAT	ATG	CAT	CAT	CAT	CAC	CAT	CAT	CTG	GTG	CCG	CGC	GGC	AGC	GCG	48
Met	His	Met	His	His	His	His	His	His	Leu	Val	Pro	Arg	Gly	Ser	Ala	
1				5					10					15		
CCC	ATC	ACG	GCC	TAC	TCC	CAA	CAG	ACG	CGG	GGC	CTA	CTT	GGT	TGC	AAG	96
Pro	Ile	Thr	Ala	Tyr	Ser	Gln	Gln	Thr	Arg	Gly	Leu	Leu	Gly	Cys	Lys	
			20					25					30			
ATC	ACT	AGC	CTT	ACA	GGC	CGG	GAC	AAG	AAC	CAG	GTC	GAG	GGA	GAG	GTT	144
Ile	Thr	Ser	Leu	Thr	Gly	Arg	Asp	Lys	Asn	Gln	Val	Glu	Gly	Glu	Val	
		35					40					45				
CAG	GTG	GTT	TCC	ACC	GCA	ACA	CAA	TCC	TTC	CTG	GCG	ACC	TGC	GTC	AAC	192
Gln	Val	Val	Ser	Thr	Ala	Thr	Gln	Ser	Phe	Leu	Ala	Thr	Cys	Val	Asn	
	50					55					60					
GGC	GTG	TGT	TGG	ACC	GTT	TAC	CAT	GGT	GCT	GGC	TCA	AAG	ACC	TTA	GCC	240
Gly	Val	Cys	Trp	Thr	Val	Tyr	His	Gly	Ala	Gly	Ser	Lys	Thr	Leu	Ala	
65					70				75					80		
GGC	CCA	AAG	GGG	CCA	ATC	ACC	CAG	ATG	TAC	ACT	AAT	GTG	GAC	CAG	GAC	288
Gly	Pro	Lys	Gly	Pro	Ile	Thr	Gln	Met	Tyr	Thr	Asn	Val	Asp	Gln	Asp	
				85					90					95		
CTC	GTC	GGC	TGG	CAG	GCG	CCC	CCC	GGG	GCG	CGT	TCC	TTG	ACA	CCA	TGC	336
Leu	Val	Gly	Trp	Gln	Ala	Pro	Pro	Gly	Ala	Arg	Ser	Leu	Thr	Pro	Cys	
			100					105					110			

ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA CAT GCT GAC GTC Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His Ala Asp Val 115 120 125	384
ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC CTG CTC TCC CCC Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro 130 135 140	432
AGG CCT GTC TCC TAC TTG AAG GGC TCT TCG GGT GGT CCA CTG CTC TGC Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly Pro Leu Leu Cys 145 150 155 160	480
CCT TCG GGG CAC GCT GTG GGC ATC TTC CGG GCT GCC GTA TGC ACC CGG Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala Val Cys Thr Arg 165 170 175	528
GGG GTT GCG AAG GCG GTG GAC TTT GTG CCC GTA GAG TCC ATG GAA ACT Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu Ser Met Glu Thr 180 185 190	576
ACT ATG CGG TCT CCG GTC TTC ACG GAC AAC TCA TCC CCC CCG GCC GTA Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser Pro Pro Ala Val 195 200 205	624
CCG CAG TCA TTT CAA GTG GCC CAC CTA CAC GCT CCC ACT GGC AGC GGC Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro Thr Gly Ser Gly 210 215 220	672
AAG AGT ACT AAA GTG CCG GCT GCA TAT GCA GCC CAA GGG TAC AAG GTG Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val 225 230 235 240	720
CTC GTC CTC AAT CCG TCC GTT GCC GCT ACC TTA GGG TTT GGG GCG TAT Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr 245 250 255	768
ATG TCT AAG GCA CAC GGT ATT GAC CCC AAC ATC AGA ACT GGG GTA AGG Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg 260 265 270	816
ACC ATT ACC ACA GGC GCC CCC GTC ACA TAC TCT ACC TAT GGC AAG TTT Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr Tyr Gly Lys Phe 275 280 285	864
CTT GCC GAT GGT GGT TGC TCT GGG GGC GCT TAT GAC ATC ATA ATA TGT Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys 290 295 300	912
GAT GAG TGC CAT TCA ACT GAC TCG ACT ACA ATC TTG GGC ATC GGC ACA Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu Gly Ile Gly Thr 305 310 315 320	960
GTC CTG GAC CAA GCG GAG ACG GCT GGA GCG CGG CTT GTC GTG CTC GCC Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala 325 330 335	1008
ACC GCT ACG CCT CCG GGA TCG GTC ACC GTG CCA CAC CCA AAC ATC GAG	1056

SUBSTITUTE SHEET (rule 26)

Thr	Ala	Thr	Pro	Pro	Gly	Ser	Val	Thr	Val	Pro	His	Pro	Asn	Ile	Glu	
			340					345					350			
GAG	GTG	GCC	CTG	TCT	AAT	ACT	GGA	GAG	ATC	CCC	TTC	TAT	GGC	AAA	GCC	1104
Glu	Val	Ala	Leu	Ser	Asn	Thr	Gly	Glu	Ile	Pro	Phe	Tyr	Gly	Lys	Ala	
		355					360				365					
ATC	CCC	ATT	GAA	GCC	ATC	AGG	GGG	GGA	AGG	CAT	CTC	ATT	TTC	TGT	CAT	1152
Ile	Pro	Ile	Glu	Ala	Ile	Arg	Gly	Gly	Arg	His	Leu	Ile	Phe	Cys	His	
	370					375				380						
TCC	AAG	AAG	AAG	TGC	GAC	GAG	CTC	GCC	GCA	AAG	CTG	TCA	GGC	CTC	GGA	1200
Ser	Lys	Lys	Lys	Cys	Asp	Glu	Leu	Ala	Ala	Lys	Leu	Ser	Gly	Leu	Gly	
385					390					395					400	
ATC	AAC	GCT	GTG	GCG	TAT	TAC	CGG	GGG	CTC	GAT	GTG	TCC	GTC	ATA	CCA	1248
Ile	Asn	Ala	Val	Ala	Tyr	Tyr	Arg	Gly	Leu	Asp	Val	Ser	Val	Ile	Pro	
			405					410						415		
ACT	ATC	GGA	GAC	GTC	GTT	GTC	GTG	GCA	ACA	GAC	GCT	CTG	ATG	ACG	GGC	1296
Thr	Ile	Gly	Asp	Val	Val	Val	Val	Ala	Thr	Asp	Ala	Leu	Met	Thr	Gly	
			420					425					430			
TAT	ACG	GGC	GAC	TTT	GAC	TCA	GTG	ATC	GAC	TGT	AAC	ACA	TGT	GTC	ACC	1344
Tyr	Thr	Gly	Asp	Phe	Asp	Ser	Val	Ile	Asp	Cys	Asn	Thr	Cys	Val	Thr	
	435					440				445						
CAG	ACA	GTC	GAC	TTC	AGC	TTG	GAT	CCC	ACC	TTC	ACC	ATT	GAG	ACG	ACG	1392
Gln	Thr	Val	Asp	Phe	Ser	Leu	Asp	Pro	Thr	Phe	Thr	Ile	Glu	Thr	Thr	
	450					455				460						
ACC	GTG	CCT	CAA	GAC	GCA	GTG	TCG	CGC	TCG	CAG	CGG	CGG	GGT	AGG	ACT	1440
Thr	Val	Pro	Gln	Asp	Ala	Val	Ser	Arg	Ser	Gln	Arg	Arg	Gly	Arg	Thr	
465					470					475					480	
GGC	AGG	GGT	AGG	AGA	GGC	ATC	TAC	AGG	TTT	GTG	ACT	CCG	GGA	GAA	CGG	1488
Gly	Arg	Gly	Arg	Arg	Gly	Ile	Tyr	Arg	Phe	Val	Thr	Pro	Gly	Glu	Arg	
			485					490						495		
CCC	TCG	GGC	ATG	TTC	GAT	TCC	TCG	GTC	CTG	TGT	GAG	TGC	TAT	GAC	GCG	1536
Pro	Ser	Gly	Met	Phe	Asp	Ser	Ser	Val	Leu	Cys	Glu	Cys	Tyr	Asp	Ala	
			500					505					510			
GGC	TGT	GCT	TGG	TAC	GAG	CTC	ACC	CCC	GCC	GAG	ACC	TCG	GTT	AGG	TTG	1584
Gly	Cys	Ala	Trp	Tyr	Glu	Leu	Thr	Pro	Ala	Glu	Thr	Ser	Val	Arg	Leu	
		515					520					525				
CGG	GCC	TAC	CTG	AAC	ACA	CCA	GGG	TTG	CCC	GTT	TGC	CAG	GAC	CAC	CTG	1632
Arg	Ala	Tyr	Leu	Asn	Thr	Pro	Gly	Leu	Pro	Val	Cys	Gln	Asp	His	Leu	
	530					535					540					
GAG	TTC	TGG	GAG	AGT	GTC	TTC	ACA	GGC	CTC	ACC	CAT	ATA	GAT	GCA	CAC	1680
Glu	Phe	Trp	Glu	Ser	Val	Phe	Thr	Gly	Leu	Thr	His	Ile	Asp	Ala	His	
545					550				555					560		
TTC	TTG	TCC	CAG	ACC	AAG	CAG	GCA	GGA	GAC	AAC	TTC	CCC	TAC	CTG	GTA	1728
Phe	Leu	Ser	Gln	Thr	Lys	Gln	Ala	Gly	Asp	Asn	Phe	Pro	Tyr	Leu	Val	
			565					570						575		

SUBSTITUTE SHEET (rule 26)

GCA TAC CAA GCC ACG GTG TGC GCC AGG GCT CAG GCC CCA CCT CCA TCA	1776
Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser	
580 585 590	
TGG GAT CAA ATG TGG AAG TGT CTC ATA CGG CTG AAA CCT ACG CTG CAC	1824
Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His	
595 600 605	
GGG CCA ACA CCC TTG CTG TAC AGG CTG GGA GCC GTC CAA AAT GAG GTC	1872
Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Val	
610 615 620	
ACC CTC ACC CAC CCC ATA ACC AAA TAC ATC ATG GCA TGC ATG TCG GCC	1920
Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala Cys Met Ser Ala	
625 630 635 640	
GAC CTG GAG GTC GTT ACG TAG GAA TTC GAG CTC CGT CGA CAA GCT TGC	1968
Asp Leu Glu Val Val Thr * Glu Phe Glu Leu Arg Arg Gln Ala Cys	
645 650 655	
GGC CGC ACT CGA GCA CCA CCA CCA CCA CCA CTG AGA TCC	2007
Gly Arg Thr Arg Ala Pro Pro Pro Pro Pro Leu Arg	
660 665	

(2) INFORMATION FOR SEQ ID NO:117:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2007 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..2004

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

ATG CAT ATG CAT CAT CAT CAC CAT CAT CTG GTG CCG CGC GGC AGC GCG	48
Met His Met His His His His His His His Leu Val Pro Arg Gly Ser Ala	
1 5 10 15	
CCC ATC ACG GCC TAC TCC CAA CAG ACG CGG GGC CTA CTT GGT TGC ATC	96
Pro Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu Leu Gly Cys Ile	
20 25 30	
AAG ACT AGC CTT ACA GGC CGG GAC AAG AAC CAG GTC GAG GGA GAG GTT	144
Lys Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val Glu Gly Glu Val	
35 40 45	

CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG ACC TGC GTC AAC	192
Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala Thr Cys Val Asn	
50 55 60	
GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA AAG ACC TTA GCC	240
Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser Lys Thr Leu Ala	
65 70 75 80	
GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT GTG GAC CAG GAC	288
Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn Val Asp Gln Asp	
85 90 95	
CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC TTG ACA CCA TGC	336
Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser Leu Thr Pro Cys	
100 105 110	
ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA CAT GCT GAC GTC	384
Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His Ala Asp Val	
115 120 125	
ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC CTG CTC TCC CCC	432
Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro	
130 135 140	
AGG CCT GTC TCC TAC TTG AAG GGC TCT TCG GGT GGT CCA CTG CTC TGC	480
Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly Pro Leu Leu Cys	
145 150 155 160	
CCT TCG GGG CAC GCT GTG GGC ATC TTC CGG GCT GCC GTA TGC ACC CGG	528
Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala Val Cys Thr Arg	
165 170 175	
GGG GTT GCG AAG GCG GTG GAC TTT GTG CCC GTA GAG TCC ATG GAA ACT	576
Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu Ser Met Glu Thr	
180 185 190	
ACT ATG CGG TCT CCG GTC TTC ACG GAC AAC TCA TCC CCC CCG GCC GTA	624
Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser Pro Pro Ala Val	
195 200 205	
CCG CAG TCA TTT CAA GTG GCC CAC CTA CAC GCT CCC ACT GGC AGC GGC	672
Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro Thr Gly Ser Gly	
210 215 220	
AAG AGT ACT AAA GTG CCG GCT GCA TAT GCA GCC CAA GGG TAC AAG GTG	720
Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val	
225 230 235 240	
CTC GTC CTC AAT CCG TCC GTT GCC GCT ACC TTA GGG TTT GGG GCG TAT	768
Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr	
245 250 255	
ATG TCT AAG GCA CAC GGT ATT GAC CCC AAC ATC AGA ACT GGG GTA AGG	816
Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg	
260 265 270	
ACC ATT ACC ACA GGC GCC CCC GTC ACA TAC TCT ACC TAT GGC AAG TTT	864
Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr Tyr Gly Lys Phe	

275	280	285	
CTT GCC GAT GGT GGT TGC TCT GGG GGC GCT TAT GAC ATC ATA ATA TGT			912
Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys			
290	295	300	
GAT GAG TGC CAT TCA ACT GAC TCG ACT ACA ATC TTG GGC ATC GGC ACA			960
Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu Gly Ile Gly Thr			
305	310	315	320
GTC CTG GAC CAA GCG GAG ACG GCT GGA GCG CGG CTT GTC GTG CTC GCC			1008
Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala			
325	330	335	
ACC GCT ACG CCT CCG GGA TCG GTC ACC GTG CCA CAC CCA AAC ATC GAG			1056
Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His Pro Asn Ile Glu			
340	345	350	
GAG GTG GCC CTG TCT AAT ACT GGA GAG ATC CCC TTC TAT GGC AAA GCC			1104
Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala			
355	360	365	
ATC CCC ATT GAA GCC ATC AGG GGG GGA AGG CAT CTC ATT TTC TGT CAT			1152
Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu Ile Phe Cys His			
370	375	380	
TCC AAG AAG AAG TGC GAC GAG CTC GCC GCA AAG CTG TCA GGC CTC GGA			1200
Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu Ser Gly Leu Gly			
385	390	395	400
ATC AAC GCT GTG GCG TAT TAC CGG GGG CTC GAT GTG TCC GTC ATA CCA			1248
Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro			
405	410	415	
ACT ATC GGA GAC GTC GTT GTC GTG GCA ACA GAC GCT CTG ATG ACG GGC			1296
Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala Leu Met Thr Gly			
420	425	430	
TAT ACG GGC GAC TTT GAC TCA GTG ATC GAC TGT AAC ACA TGT GTC ACC			1344
Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr			
435	440	445	
CAG ACA GTC GAC TTC AGC TTG GAT CCC ACC TTC ACC ATT GAG ACG ACG			1392
Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr			
450	455	460	
ACC GTG CCT CAA GAC GCA GTG TCG CGC TCG CAG CGG CGG GGT AGG ACT			1440
Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg Arg Gly Arg Thr			
465	470	475	480
GGC AGG GGT AGG AGA GGC ATC TAC AGG TTT GTG ACT CCG GGA GAA CGG			1488
Gly Arg Gly Arg Arg Gly Ile Tyr Arg Phe Val Thr Pro Gly Glu Arg			
485	490	495	
CCC TCG GGC ATG TTC GAT TCC TCG GTC CTG TGT GAG TGC TAT GAC GCG			1536
Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala			
500	505	510	

GGC TGT GCT TGG TAC GAG CTC ACC CCC GCC GAG ACC TCG GTT AGG TTG	1584
Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr Ser Val Arg Leu	
515 520 525	
CGG GCC TAC CTG AAC ACA CCA GGG TTG CCC GTT TGC CAG GAC CAC CTG	1632
Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu	
530 535 540	
GAG TTC TGG GAG AGT GTC TTC ACA GGC CTC ACC CAT ATA GAT GCA CAC	1680
Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His Ile Asp Ala His	
545 550 555 560	
TTC TTG TCC CAG ACC AAG CAG GCA GGA GAC AAC TTC CCC TAC CTG GTA	1728
Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe Pro Tyr Leu Val	
565 570 575	
GCA TAC CAA GCC ACG GTG TGC GCC AGG GCT CAG GCC CCA CCT CCA TCA	1776
Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser	
580 585 590	
TGG GAT CAA ATG TGG AAG TGT CTC ATA CGG CTG AAA CCT ACG CTG CAC	1824
Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His	
595 600 605	
GGG CCA ACA CCC TTG CTG TAC AGG CTG GGA GCC GTC CAA AAT GAG GTC	1872
Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Val	
610 615 620	
ACC CTC ACC CAC CCC ATA ACC AAA TAC ATC ATG GCA TGC ATG TCG GCC	1920
Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala Cys Met Ser Ala	
625 630 635 640	
GAC CTG GAG GTC GTT ACG TAG GAA TTC GAG CTC CGT CGA CAA GCT TGC	1968
Asp Leu Glu Val Val Thr * Glu Phe Glu Leu Arg Arg Gln Ala Cys	
645 650 655	
GGC CGC ACT CGA GCA CCA CCA CCA CCA CCA CTG AGA TCC	2007
Gly Arg Thr Arg Ala Pro Pro Pro Pro Pro Leu Arg	
660 665	

(2) INFORMATION FOR SEQ ID NO:118:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2007 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..2004

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

ATG CAT ATG CAT CAT CAT CAC CAT CAT CTG GTG CCG CGC GGC AGC GCG Met His Met His His His His His His Leu Val Pro Arg Gly Ser Ala 1 5 10 15	48
CCC ATC ACG GCC TAC TCC CAA CAG ACG CGG GGC CTA CTT GGT TGC ATC Pro Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu Leu Gly Cys Ile 20 25 30	96
ATC ACT AGC CTT ACA GGC CGG GAC AAG AAC CAG GTC GAG GGA GAG GTT Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val Glu Gly Glu Val 35 40 45	144
CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG ACC TGC GTC AAC Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala Thr Cys Val Asn 50 55 60	192
GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA AAG ACC TTA GCC Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser Lys Thr Leu Ala 65 70 75 80	240
GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT GTG GAC CAG GAC Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn Val Asp Gln Asp 85 90 95	288
CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC TTG ACA CCA TGC Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser Leu Thr Pro Cys 100 105 110	336
ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA CAT GCT GAC GTC Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His Ala Asp Val 115 120 125	384
ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC CTG CTC TCC CCC Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro 130 135 140	432
AGG CCT GTC TCC TAC TTG AAG GGC TCT GCT GGT GGT CCA CTG CTC TGC Arg Pro Val Ser Tyr Leu Lys Gly Ser Ala Gly Gly Pro Leu Leu Cys 145 150 155 160	480
CCT TCG GGG CAC GCT GTG GGC ATC TTC CGG GCT GCC GTA TGC ACC CGG Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala Val Cys Thr Arg 165 170 175	528
GGG GTT GCG AAG GCG GTG GAC TTT GTG CCC GTA GAG TCC ATG GAA ACT Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu Ser Met Glu Thr 180 185 190	576
ACT ATG CGG TCT CCG GTC TTC ACG GAC AAC TCA TCC CCC CCG GCC GTA Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser Pro Pro Ala Val 195 200 205	624
CCG CAG TCA TTT CAA GTG GCC CAC CTA CAC GCT CCC ACT GGC AGC GGC Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro Thr Gly Ser Gly 210 215 220	672
AAG AGT ACT AAA GTG CCG GCT GCA TAT GCA GCC CAA GGG TAC AAG GTG	720

Lys 225	Ser	Thr	Lys	Val	Pro 230	Ala	Ala	Tyr	Ala	Ala 235	Gln	Gly	Tyr	Lys	Val 240	
CTC	GTC	CTC	AAT	CCG	TCC	GTT	GCC	GCT	ACC	TTA	GGG	TTT	GGG	GCG	TAT	768
Leu	Val	Leu	Asn	Pro	Ser	Val	Ala	Ala	Thr	Leu	Gly	Phe	Gly	Ala	Tyr	
			245						250					255		
ATG	TCT	AAG	GCA	CAC	GGT	ATT	GAC	CCC	AAC	ATC	AGA	ACT	GGG	GTA	AGG	816
Met	Ser	Lys	Ala	His	Gly	Ile	Asp	Pro	Asn	Ile	Arg	Thr	Gly	Val	Arg	
			260					265					270			
ACC	ATT	ACC	ACA	GGC	GCC	CCC	GTC	ACA	TAC	TCT	ACC	TAT	GGC	AAG	TTT	864
Thr	Ile	Thr	Thr	Gly	Ala	Pro	Val	Thr	Tyr	Ser	Thr	Tyr	Gly	Lys	Phe	
			275				280						285			
CTT	GCC	GAT	GGT	GGT	TGC	TCT	GGG	GGC	GCT	TAT	GAC	ATC	ATA	ATA	TGT	912
Leu	Ala	Asp	Gly	Gly	Cys	Ser	Gly	Gly	Ala	Tyr	Asp	Ile	Ile	Ile	Cys	
	290					295					300					
GAT	GAG	TGC	CAT	TCA	ACT	GAC	TCG	ACT	ACA	ATC	TTG	GGC	ATC	GGC	ACA	960
Asp	Glu	Cys	His	Ser	Thr	Asp	Ser	Thr	Thr	Ile	Leu	Gly	Ile	Gly	Thr	
305					310					315					320	
GTC	CTG	GAC	CAA	GCG	GAG	ACG	GCT	GGA	GCG	CGG	CTT	GTC	GTG	CTC	GCC	1008
Val	Leu	Asp	Gln	Ala	Glu	Thr	Ala	Gly	Ala	Arg	Leu	Val	Val	Leu	Ala	
			325					330						335		
ACC	GCT	ACG	CCT	CCG	GGA	TCG	GTC	ACC	GTG	CCA	CAC	CCA	AAC	ATC	GAG	1056
Thr	Ala	Thr	Pro	Pro	Gly	Ser	Val	Thr	Val	Pro	His	Pro	Asn	Ile	Glu	
			340					345					350			
GAG	GTG	GCC	CTG	TCT	AAT	ACT	GGA	GAG	ATC	CCC	TTC	TAT	GGC	AAA	GCC	1104
Glu	Val	Ala	Leu	Ser	Asn	Thr	Gly	Glu	Ile	Pro	Phe	Tyr	Gly	Lys	Ala	
	355						360					365				
ATC	CCC	ATT	GAA	GCC	ATC	AGG	GGG	GGA	AGG	CAT	CTC	ATT	TTC	TGT	CAT	1152
Ile	Pro	Ile	Glu	Ala	Ile	Arg	Gly	Gly	Arg	His	Leu	Ile	Phe	Cys	His	
	370					375					380					
TCC	AAG	AAG	AAG	TGC	GAC	GAG	CTC	GCC	GCA	AAG	CTG	TCA	GGC	CTC	GGA	1200
Ser	Lys	Lys	Lys	Cys	Asp	Glu	Leu	Ala	Ala	Lys	Leu	Ser	Gly	Leu	Gly	
385					390					395					400	
ATC	AAC	GCT	GTG	GCG	TAT	TAC	CGG	GGG	CTC	GAT	GTG	TCC	GTC	ATA	CCA	1248
Ile	Asn	Ala	Val	Ala	Tyr	Tyr	Arg	Gly	Leu	Asp	Val	Ser	Val	Ile	Pro	
			405					410						415		
ACT	ATC	GGA	GAC	GTC	GTT	GTC	GTG	GCA	ACA	GAC	GCT	CTG	ATG	ACG	GGC	1296
Thr	Ile	Gly	Asp	Val	Val	Val	Val	Ala	Thr	Asp	Ala	Leu	Met	Thr	Gly	
			420					425					430			
TAT	ACG	GGC	GAC	TTT	GAC	TCA	GTG	ATC	GAC	TGT	AAC	ACA	TGT	GTC	ACC	1344
Tyr	Thr	Gly	Asp	Phe	Asp	Ser	Val	Ile	Asp	Cys	Asn	Thr	Cys	Val	Thr	
		435					440					445				
CAG	ACA	GTC	GAC	TTC	AGC	TTG	GAT	CCC	ACC	TTC	ACC	ATT	GAG	ACG	ACG	1392
Gln	Thr	Val	Asp	Phe	Ser	Leu	Asp	Pro	Thr	Phe	Thr	Ile	Glu	Thr	Thr	
	450					455					460					

ACC GTG CCT CAA GAC GCA GTG TCG CGC TCG CAG CGG CGG GGT AGG ACT	1440
Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg Arg Gly Arg Thr	
465 470 475 480	
GGC AGG GGT AGG AGA GGC ATC TAC AGG TTT GTG ACT CCG GGA GAA CGG	1488
Gly Arg Gly Arg Arg Gly Ile Tyr Arg Phe Val Thr Pro Gly Glu Arg	
485 490 495	
CCC TCG GGC ATG TTC GAT TCC TCG GTC CTG TGT GAG TGC TAT GAC GCG	1536
Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala	
500 505 510	
GGC TGT GCT TGG TAC GAG CTC ACC CCC GCC GAG ACC TCG GTT AGG TTG	1584
Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr Ser Val Arg Leu	
515 520 525	
CGG GCC TAC CTG AAC ACA CCA GGG TTG CCC GTT TGC CAG GAC CAC CTG	1632
Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu	
530 535 540	
GAG TTC TGG GAG AGT GTC TTC ACA GGC CTC ACC CAT ATA GAT GCA CAC	1680
Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His Ile Asp Ala His	
545 550 555 560	
TTC TTG TCC CAG ACC AAG CAG GCA GGA GAC AAC TTC CCC TAC CTG GTA	1728
Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe Pro Tyr Leu Val	
565 570 575	
GCA TAC CAA GCC ACG GTG TGC GCC AGG GCT CAG GCC CCA CCT CCA TCA	1776
Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser	
580 585 590	
TGG GAT CAA ATG TGG AAG TGT CTC ATA CGG CTG AAA CCT ACG CTG CAC	1824
Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His	
595 600 605	
GGG CCA ACA CCC TTG CTG TAC AGG CTG GGA GCC GTC CAA AAT GAG GTC	1872
Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Val	
610 615 620	
ACC CTC ACC CAC CCC ATA ACC AAA TAC ATC ATG GCA TGC ATG TCG GCC	1920
Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala Cys Met Ser Ala	
625 630 635 640	
GAC CTG GAG GTC GTT ACG TAG GAA TTC GAG CTC CGT CGA CAA GCT TGC	1968
Asp Leu Glu Val Val Thr * Glu Phe Glu Leu Arg Arg Gln Ala Cys	
645 650 655	
GGC CGC ACT CGA GCA CCA CCA CCA CCA CCA CTG AGA TCC	2007
Gly Arg Thr Arg Ala Pro Pro Pro Pro Pro Leu Arg	
660 665	

(2) INFORMATION FOR SEQ ID NO:119:

(i) SEQUENCE CHARACTERISTICS:

SUBSTITUTE SHEET (rule 26)

- (A) LENGTH: 2007 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
 (B) LOCATION: 1..2004

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

ATG CAT ATG CAT CAT CAT CAC CAT CAT CTG GTG CCG CGC GGC AGC GCG	48
Met His Met His His His His His His Leu Val Pro Arg Gly Ser Ala	
1 5 10 15	
CCC ATC ACG GCC TAC TCC CAA CAG ACG CGG GGC CTA CTT GGT TGC ATC	96
Pro Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu Leu Gly Cys Ile	
20 25 30	
ATC ACT AGC CTT ACA GGC CGG GAC AAG AAC CAG GTC GAG GGA GAG GTT	144
Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val Glu Gly Glu Val	
35 40 45	
CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG ACC TGC GTC AAC	192
Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala Thr Cys Val Asn	
50 55 60	
GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA AAG ACC TTA GCC	240
Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser Lys Thr Leu Ala	
65 70 75 80	
GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT GTG GAC CAG GAC	288
Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn Val Asp Gln Asp	
85 90 95	
CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC TTG ACA CCA TGC	336
Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser Leu Thr Pro Cys	
100 105 110	
ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA CAT GCT GAC GTC	384
Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His Ala Asp Val	
115 120 125	
ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC CTG CTC TCC CCC	432
Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro	
130 135 140	
AGG CCT GTC TCC TAC TTG AAG GGC TCT TCG GGT GGT CCA CTG CTC TGC	480
Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly Pro Leu Leu Cys	
145 150 155 160	
CCT TCG GGG CAC GCT GTG GGC ATC TTC CGG GCT GCC GTA TGC ACC CGG	528
Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala Val Cys Thr Arg	
165 170 175	

SUBSTITUTE SHEET (rule 26)

GGG GTT GCG AAG GCG GTG GAC TTT GTG CCC GTA GAG TCC ATG GAA ACT Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu Ser Met Glu Thr 180 185 190	576
ACT ATG CGG TCT CCG GTC TTC ACG GAC AAC TCA TCC CCC CCG GCC GTA Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser Pro Pro Ala Val 195 200 205	624
CCG CAG TCA TTT CAA GTG GCC CAC CTA CAC GCT CCC ACT GGC AGC GGC Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro Thr Gly Ser Gly 210 215 220	672
AAG AGT ACT AAA GTG CCG GCT GCA TAT GCA GCC CAA GGG TAC AAG GTG Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val 225 230 235 240	720
CTC GTC CTC AAT CCG TCC GTT GCC GCT ACC TTA GGG TTT GGG GCG TAT Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr 245 250 255	768
ATG TCT AAG GCA CAC GGT ATT GAC CCC AAC ATC AGA ACT GGG GTA AGG Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg 260 265 270	816
ACC ATT ACC ACA GGC GCC CCC GTC ACA TAC TCT ACC TAT GGC AAG TTT Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr Tyr Gly Lys Phe 275 280 285	864
CTT GCC GAT GGT GGT TGC TCT GGG GGC GCT TAT GAC ATC ATA ATA TGT Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys 290 295 300	912
GAT GAG TGC CAT TCA ACT GAC TCG ACT ACA ATC TTG GGC ATC GGC ACA Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu Gly Ile Gly Thr 305 310 315 320	960
GTC CTG GAC CAA GCG GAG ACG GCT GGA GCG CGG CTT GTC GTG CTC GCC Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala 325 330 335	1008
ACC GCT ACG CCT CCG GGA TCG GTC ACC GTG CCA CAC CCA AAC ATC GAG Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His Pro Asn Ile Glu 340 345 350	1056
GAG GTG GCC CTG TCT AAT ACT GGA GAG ATC CCC TTC TAT GGC AAA GCC Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala 355 360 365	1104
ATC CCC ATT GAA GCC ATC AGG GGG GGA AGG CAT CTC ATT TTC TGT CAT Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu Ile Phe Cys His 370 375 380	1152
TCC AAG AAG AAG TGC GAC GAG CTC GCC GCA AAG CTG TCA GGC CTC GGA Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu Ser Gly Leu Gly 385 390 395 400	1200
ATC AAC GCT GTG GCG TAT TAC CGG GGG CTC GAT GTG TCC GTC ATA CCA	1248

SUBSTITUTE SHEET (rule 26)

Ile	Asn	Ala	Val	Ala	Tyr	Tyr	Arg	Gly	Leu	Asp	Val	Ser	Val	Ile	Pro	
				405					410					415		
ACT	TCC	GGA	GAC	GTC	GTT	GTC	GTG	GCA	ACA	GAC	GCT	CTG	ATG	ACG	GGC	1296
Thr	Ser	Gly	Asp	Val	Val	Val	Val	Ala	Thr	Asp	Ala	Leu	Met	Thr	Gly	
			420					425				430				
TAT	ACG	GGC	GAC	TTT	GAC	TCA	GTG	ATC	GAC	TGT	AAC	ACA	TGT	GTC	ACC	1344
Tyr	Thr	Gly	Asp	Phe	Asp	Ser	Val	Ile	Asp	Cys	Asn	Thr	Cys	Val	Thr	
			435				440					445				
CAG	ACA	GTC	GAC	TTC	AGC	TTG	GAT	CCC	ACC	TTC	ACC	ATT	GAG	ACG	ACG	1392
Gln	Thr	Val	Asp	Phe	Ser	Leu	Asp	Pro	Thr	Phe	Thr	Ile	Glu	Thr	Thr	
			450				455					460				
ACC	GTG	CCT	CAA	GAC	GCA	GTG	TCG	CGC	TCG	CAG	CGG	CGG	GGT	AGG	ACT	1440
Thr	Val	Pro	Gln	Asp	Ala	Val	Ser	Arg	Ser	Gln	Arg	Arg	Gly	Arg	Thr	
465					470					475					480	
GGC	AGG	GGT	AGG	AGA	GGC	ATC	TAC	AGG	TTT	GTG	ACT	CCG	GGA	GAA	CGG	1488
Gly	Arg	Gly	Arg	Arg	Gly	Ile	Tyr	Arg	Phe	Val	Thr	Pro	Gly	Glu	Arg	
				485					490					495		
CCC	TCG	GGC	ATG	TTC	GAT	TCC	TCG	GTC	CTG	TGT	GAG	TGC	TAT	GAC	GCG	1536
Pro	Ser	Gly	Met	Phe	Asp	Ser	Ser	Val	Leu	Cys	Glu	Cys	Tyr	Asp	Ala	
			500					505						510		
GGC	TGT	GCT	TGG	TAC	GAG	CTC	ACC	CCC	GCC	GAG	ACC	TCG	GTT	AGG	TTG	1584
Gly	Cys	Ala	Trp	Tyr	Glu	Leu	Thr	Pro	Ala	Glu	Thr	Ser	Val	Arg	Leu	
			515				520					525				
CGG	GCC	TAC	CTG	AAC	ACA	CCA	GGG	TTG	CCC	GTT	TGC	CAG	GAC	CAC	CTG	1632
Arg	Ala	Tyr	Leu	Asn	Thr	Pro	Gly	Leu	Pro	Val	Cys	Gln	Asp	His	Leu	
			530				535					540				
GAG	TTC	TGG	GAG	AGT	GTC	TTC	ACA	GGC	CTC	ACC	CAT	ATA	GAT	GCA	CAC	1680
Glu	Phe	Trp	Glu	Ser	Val	Phe	Thr	Gly	Leu	Thr	His	Ile	Asp	Ala	His	
545					550					555					560	
TTC	TTG	TCC	CAG	ACC	AAG	CAG	GCA	GGA	GAC	AAC	TTC	CCC	TAC	CTG	GTA	1728
Phe	Leu	Ser	Gln	Thr	Lys	Gln	Ala	Gly	Asp	Asn	Phe	Pro	Tyr	Leu	Val	
				565					570					575		
GCA	TAC	CAA	GCC	ACG	GTG	TGC	GCC	AGG	GCT	CAG	GCC	CCA	CCT	CCA	TCA	1776
Ala	Tyr	Gln	Ala	Thr	Val	Cys	Ala	Arg	Ala	Gln	Ala	Pro	Pro	Pro	Ser	
			580					585						590		
TGG	GAT	CAA	ATG	TGG	AAG	TGT	CTC	ATA	CGG	CTG	AAA	CCT	ACG	CTG	CAC	1824
Trp	Asp	Gln	Met	Trp	Lys	Cys	Leu	Ile	Arg	Leu	Lys	Pro	Thr	Leu	His	
			595				600					605				
GGG	CCA	ACA	CCC	TTG	CTG	TAC	AGG	CTG	GGA	GCC	GTC	CAA	AAT	GAG	GTC	1872
Gly	Pro	Thr	Pro	Leu	Leu	Tyr	Arg	Leu	Gly	Ala	Val	Gln	Asn	Glu	Val	
			610				615				620					
ACC	CTC	ACC	CAC	CCC	ATA	ACC	AAA	TAC	ATC	ATG	GCA	TGC	ATG	TCG	GCC	1920
Thr	Leu	Thr	His	Pro	Ile	Thr	Lys	Tyr	Ile	Met	Ala	Cys	Met	Ser	Ala	
625					630					635					640	

SUBSTITUTE SHEET (rule 26)

GAC CTG GAG GTC GTT ACG TAG GAA TTC GAG CTC CGT CGA CAA GCT TGC 1968
 Asp Leu Glu Val Val Thr * Glu Phe Glu Leu Arg Arg Gln Ala Cys
 645 650 655

GGC CGC ACT CGA GCA CCA CCA CCA CCA CCA CTG AGA TCC 2007
 Gly Arg Thr Arg Ala Pro Pro Pro Pro Pro Leu Arg
 660 665

(2) INFORMATION FOR SEQ ID NO:120:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2007 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..2007

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:

ATG CAT ATG CAT CAT CAT CAC CAT CAT CTG GTG CCG CGC GGC AGC GCG 48
 Met His Met His His His His His His Leu Val Pro Arg Gly Ser Ala
 1 5 10 15

CCC ATC ACG GCC TAC TCC CAA CAG ACG CGG GGC CTA CTT GGT TGC ATC 96
 Pro Ile Thr Ala Tyr Ser Gln Gln Thr Arg Gly Leu Leu Gly Cys Ile
 20 25 30

ATC ACT AGC CTT ACA GGC CGG GAC AAG AAC CAG GTC GAG GGA GAG GTT 144
 Ile Thr Ser Leu Thr Gly Arg Asp Lys Asn Gln Val Glu Gly Glu Val
 35 40 45

CAG GTG GTT TCC ACC GCA ACA CAA TCC TTC CTG GCG ACC TGC GTC AAC 192
 Gln Val Val Ser Thr Ala Thr Gln Ser Phe Leu Ala Thr Cys Val Asn
 50 55 60

GGC GTG TGT TGG ACC GTT TAC CAT GGT GCT GGC TCA AAG ACC TTA GCC 240
 Gly Val Cys Trp Thr Val Tyr His Gly Ala Gly Ser Lys Thr Leu Ala
 65 70 75 80

GGC CCA AAG GGG CCA ATC ACC CAG ATG TAC ACT AAT GTG GAC CAG GAC 288
 Gly Pro Lys Gly Pro Ile Thr Gln Met Tyr Thr Asn Val Asp Gln Asp
 85 90 95

CTC GTC GGC TGG CAG GCG CCC CCC GGG GCG CGT TCC TTG ACA CCA TGC 336
 Leu Val Gly Trp Gln Ala Pro Pro Gly Ala Arg Ser Leu Thr Pro Cys
 100 105 110

ACC TGT GGC AGC TCA GAC CTT TAC TTG GTC ACG AGA CAT GCT GAC GTC 384
 Thr Cys Gly Ser Ser Asp Leu Tyr Leu Val Thr Arg His Ala Asp Val

115	120	125	
ATT CCG GTG CGC CGG CGG GGC GAC AGT AGG GGG AGC CTG CTC TCC CCC Ile Pro Val Arg Arg Arg Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro 130 135 140			432
AGG CCT GTC TCC TAC TTG AAG GGC TCT TCG GGT GGT CCA CTG CTC TGC Arg Pro Val Ser Tyr Leu Lys Gly Ser Ser Gly Gly Pro Leu Leu Cys 145 150 155 160			480
CCT TCG GGG CAC GCT GTG GGC ATC TTC CGG GCT GCC GTA TGC ACC CGG Pro Ser Gly His Ala Val Gly Ile Phe Arg Ala Ala Val Cys Thr Arg 165 170 175			528
GGG GTT GCG AAG GCG GTG GAC TTT GTG CCC GTA GAG TCC ATG GAA ACT Gly Val Ala Lys Ala Val Asp Phe Val Pro Val Glu Ser Met Glu Thr 180 185 190			576
ACT ATG CGG TCT CCG GTC TTC ACG GAC AAC TCA TCC CCC CCG GCC GTA Thr Met Arg Ser Pro Val Phe Thr Asp Asn Ser Ser Pro Pro Ala Val 195 200 205			624
CCG CAG TCA TTT CAA GTG GCC CAC CTA CAC GCT CCC ACT GGC AGC GGC Pro Gln Ser Phe Gln Val Ala His Leu His Ala Pro Thr Gly Ser Gly 210 215 220			672
AAG AGT ACT AAA GTG CCG GCT GCC TAC GCA GCC CAA GGG TAC AAG GTG Lys Ser Thr Lys Val Pro Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val 225 230 235 240			720
CTC GTC CTC AAT CCG TCC GTT GCC GCT ACC TTA GGG TTT GGG GCG TAT Leu Val Leu Asn Pro Ser Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr 245 250 255			768
ATG TCT AAG GCA CAC GGT ATT GAC CCC AAC ATC AGA ACT GGG GTA AGG Met Ser Lys Ala His Gly Ile Asp Pro Asn Ile Arg Thr Gly Val Arg 260 265 270			816
ACC ATT ACC ACA GGC GCC CCC GTC ACA TAC TCT ACC TAT GGC AAG TTT Thr Ile Thr Thr Gly Ala Pro Val Thr Tyr Ser Thr Tyr Gly Lys Phe 275 280 285			864
CTT GCC GAT GGT GGT TGC TCT GGG GGC GCT TAT GAC ATC ATA ATA TGT Leu Ala Asp Gly Gly Cys Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys 290 295 300			912
GAT GAG TGC CAT TCA ACT GAC TCG ACT ACA ATC TTG GGC ATC GGC ACA Asp Glu Cys His Ser Thr Asp Ser Thr Thr Ile Leu Gly Ile Gly Thr 305 310 315 320			960
GTC CTG GAC CAA GCG GAG ACG GCT GGA GCG CGG CTT GTC GTG CTC GCC Val Leu Asp Gln Ala Glu Thr Ala Gly Ala Arg Leu Val Val Leu Ala 325 330 335			1008
ACC GCT ACG CCT CCG GGA TCG GTC ACC GTG CCA CAC CCA AAC ATC GAG Thr Ala Thr Pro Pro Gly Ser Val Thr Val Pro His Pro Asn Ile Glu 340 345 350			1056

SUBSTITUTE SHEET (rule 26)

GAG GTG GCC CTG TCT AAT ACT GGA GAG ATC CCC TTC TAT GGC AAA GCC Glu Val Ala Leu Ser Asn Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala 355 360 365	1104
ATC CCC ATT GAA GCC ATC AGG GGG GGA AGG CAT CTC ATT TTC TGT CAT Ile Pro Ile Glu Ala Ile Arg Gly Gly Arg His Leu Ile Phe Cys His 370 375 380	1152
TCC AAG AAG AAG TGC GAC GAG CTC GCC GCA AAG CTG TCA GGC CTC GGA Ser Lys Lys Lys Cys Asp Glu Leu Ala Ala Lys Leu Ser Gly Leu Gly 385 390 395 400	1200
ATC AAC GCT GTG GCG TAT TAC CGG GGG CTC GAT GTG TCC GTC ATA CCA Ile Asn Ala Val Ala Tyr Tyr Arg Gly Leu Asp Val Ser Val Ile Pro 405 410 415	1248
ACT ATC GGA GAC GTC GTT GTC GTG GCA ACA GAC GCT CTG ATG ACG GGC Thr Ile Gly Asp Val Val Val Val Ala Thr Asp Ala Leu Met Thr Gly 420 425 430	1296
TAT ACG GGC GAC TTT GAC TCA GTG ATC GAC TGT AAC ACA TGT GTC ACC Tyr Thr Gly Asp Phe Asp Ser Val Ile Asp Cys Asn Thr Cys Val Thr 435 440 445	1344
CAG ACA GTC GAC TTC AGC TTG GAT CCC ACC TTC ACC ATT GAG ACG ACG Gln Thr Val Asp Phe Ser Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr 450 455 460	1392
ACC GTG CCT CAA GAC GCA GTG TCG CGC TCG CAG CGG CGG GGT AGG ACT Thr Val Pro Gln Asp Ala Val Ser Arg Ser Gln Arg Arg Gly Arg Thr 465 470 475 480	1440
GGC AGG GGT AGG AGA GGC ATC TAC AGG TTT GTG ACT CCG GGA GAA CGG Gly Arg Gly Arg Arg Gly Ile Tyr Arg Phe Val Thr Pro Gly Glu Arg 485 490 495	1488
CCC TCG GGC ATG TTC GAT TCC TCG GTC CTG TGT GAG TGC TAT GAC GCG Pro Ser Gly Met Phe Asp Ser Ser Val Leu Cys Glu Cys Tyr Asp Ala 500 505 510	1536
GGC TGT GCT TGG TAC GAG CTC ACC CCC GCC GAG ACC TCG GTT AGG TTG Gly Cys Ala Trp Tyr Glu Leu Thr Pro Ala Glu Thr Ser Val Arg Leu 515 520 525	1584
CGG GCC TAC CTG AAC ACA CCA GGG TTG CCC GTT TGC CAG GAC CAC CTG Arg Ala Tyr Leu Asn Thr Pro Gly Leu Pro Val Cys Gln Asp His Leu 530 535 540	1632
GAG TTC TGG GAG AGT GTC TTC ACA GGC CTC ACC CAT ATA GAT GCA CAC Glu Phe Trp Glu Ser Val Phe Thr Gly Leu Thr His Ile Asp Ala His 545 550 555 560	1680
TTC TTG TCC CAG ACC AAG CAG GCA GGA GAC AAC TTC CCC TAC CTG GTA Phe Leu Ser Gln Thr Lys Gln Ala Gly Asp Asn Phe Pro Tyr Leu Val 565 570 575	1728
GCA TAC CAA GCC ACG GTG TGC GCC AGG GCT CAG GCC CCA CCT CCA TCA Ala Tyr Gln Ala Thr Val Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser 580 585 590 595 600	1776

580	585	590	
TGG GAT CAA ATG TGG AAG TGT CTC ATA CGG CTG AAA CCT ACG CTG CAC			1824
Trp Asp Gln Met Trp Lys Cys Leu Ile Arg Leu Lys Pro Thr Leu His			
595	600	605	
GGG CCA ACA CCC TTG CTG TAC AGG CTG GGA GCC GTC CAA AAT GAG GTC			1872
Gly Pro Thr Pro Leu Leu Tyr Arg Leu Gly Ala Val Gln Asn Glu Val			
610	615	620	
ACC CTC ACC CAC CCC ATA ACC AAA TAC ATC ATG GCA TGC ATG TCG GCC			1920
Thr Leu Thr His Pro Ile Thr Lys Tyr Ile Met Ala Cys Met Ser Ala			
625	630	635	640
GAC CTG GAG GTC GTT ACG TAG GAA TTC GAG CTC CGT CGA CAA GCT TGC			1968
Asp Leu Glu Val Val Thr * Glu Phe Glu Leu Arg Arg Gln Ala Cys			
645	650	655	
GGC CGC ACT CGA GCA CCA CCA CCA CCA CCA CTG AGA TCC			2007
Gly Arg Thr Arg Ala Pro Pro Pro Pro Pro Leu Arg Ser			
660	665		

(2) INFORMATION FOR SEQ ID NO:121:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: RNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:

GCUCGCCCCGG GGAUCCUCUA GGAAUACACG UUCGAU 36

(2) INFORMATION FOR SEQ ID NO:122:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: RNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

CUAGAGGAUC CCCGGGCGAG CCCUAUAGUG AGUCGU 36

(2) INFORMATION FOR SEQ ID NO:123:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 21 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

GCTCGCCCGG GGATCCTCTA G

21

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: C12N 15/62, C07K 19/00, C12N 1/21, 5/10, C12Q 1/37, 1/533 // C07K 14/18, C12N 9/50	A3	(11) International Publication Number: WO 99/28482 (43) International Publication Date: 10 June 1999 (10.06.99)
(21) International Application Number: PCT/US98/24528 (22) International Filing Date: 24 November 1998 (24.11.98) (30) Priority Data: 60/067,315 28 November 1997 (28.11.97) US 60/094,331 28 July 1998 (28.07.98) US (71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US). (72) Inventors: MALCOLM, Bruce, A.; 515 Trinity Place, Westfield, NJ 07090 (US). TAREMI, S., Shane; 12 Park Terrace, Upper Montclair, NJ 07043 (US). WEBER, Patricia, C.; 1970 Timber Lakes Drive, Yardley, PA 19067 (US). YAO, Nanhua; 4 Timothy Court, Edison, NJ 08837 (US). (74) Agents: McLAUGHLIN, Jaye, P. et al.; Schering-Plough Corporation, Patent Dept., K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GD, GE, HR, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 22 July 1999 (22.07.99)
(54) Title: SINGLE-CHAIN RECOMBINANT COMPLEXES OF HEPATITIS C VIRUS NS3 PROTEASE AND NS4A COFACTOR PEPTIDE (57) Abstract Covalent HCV NS4A-NS3 complexes comprising the central hydrophobic domain of native HCV NS4A peptide, a linker, and the HCV NS3 serine protease domain, wherein the hydrophobic domain of native HCV NS4A peptide is tethered by the linker to the amino terminus of the HCV NS3 protease domain.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/24528

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/62 C07K19/00 C12N1/21 C12N5/10 C12Q1/37
C12Q1/533 //C07K14/18, C12N9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 36702 A (SCHERING CORP) 21 November 1996 see example 6 sequence 7	1, 12, 23-26
Y	KIM J L ET AL: "CRYSTAL STRUCTURE OF THE HEPATITIS C VIRUS NS3 PROTEASE DOMAIN COMPLEXED WITH A SYNTHETIC NS4A COFACTOR PEPTIDE" CELL, vol. 87, no. 4, 18 October 1996, pages 343-355, XP002053693 cited in the application see page 348, right-hand column, paragraph 2 - page 350, left-hand column see conclusions	1, 12, 23-26



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

25 May 1999

Date of mailing of the international search report

04/06/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Van der Schaal, C

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/24528

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	<p>YAN Y ET AL: "Complex of NS3 protease and NS4 peptide of BK strain hepatitis C virus: " PROTEIN SCIENCE, vol. 7, no. 4, April 1998, pages 837-847, XP002103543 see the whole document</p> <p style="text-align: center;">---</p>	1,12, 23-26
Y	<p>BARTENSCHLAGER R ET AL: "COMPLEX FORMATION BETWEEN THE NS3 SERINE-TYPE PROTEINASE OF THE HEPATITIS C VIRUS AND NS4A AND ITS IMPORTANCE FOR POLYPROTEIN MATURATION" JOURNAL OF VIROLOGY, vol. 69, no. 12, 1 December 1995, pages 7519-7528, XP002053692 see page 7527, left-hand column, paragraph 2</p> <p style="text-align: center;">---</p>	1,12, 23-26
A	<p>WO 97 08304 A (ANGELETTI P IST RICHERCHE BIO ;FRANCESCO RAFFAELE DE (IT); TOMEI L) 6 March 1997 see sequence 4</p> <p style="text-align: center;">---</p>	
A	<p>LIN C ET AL: "HEPATITIS C VIRUS NS3 SERINE PROTEINASE: TRANS-CLEAVAGE REQUIREMENTS AND PROCESSING KINETICS" JOURNAL OF VIROLOGY, vol. 68, no. 12, 1 December 1994, pages 8147-8157, XP002012002 see abstract; figure 9</p> <p style="text-align: center;">---</p>	
Y	<p>KIM D W ET AL: "C-TERMINAL DOMAIN OF THE HEPATITIS C VIRUS NS3 PROTEIN CONTAINS AN RNA HELICASE ACTIVITY" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 215, no. 1, 4 October 1995, pages 160-166, XP002035618 cited in the application see the whole document</p> <p style="text-align: center;">---</p>	27,28
P,X	<p>TAREMI S S ET AL: "Construction, expression, and characterization of a novel fully activated recombinant single-chain hepatitis C virus protease." PROTEIN SCIENCE, (1998 OCT) 7 (10) 2143-9. JOURNAL CODE: BNW. ISSN: 0961-8368., XP002103544 United States</p> <p style="text-align: center;">---</p>	1-6, 12-17, 23-26
Y	<p>see the whole document</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	27,28

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/24528

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	<p>DIMASI N ET AL: "Engineering, characterization and phage display of hepatitis C virus NS3 protease and NS4A cofactor peptide as a single-chain protein."</p> <p>PROTEIN ENGINEERING, (1998 DEC) 11 (12) 1257-65. JOURNAL CODE: PR1. ISSN: 0269-2139., XP002103545</p> <p>ENGLAND: United Kingdom</p> <p>see the whole document</p> <p>-----</p>	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/24528

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9636702 A	21-11-1996	US 5843752 A	01-12-1998
		AU 5729196 A	29-11-1996
		CA 2220575 A	21-11-1996
		EP 0826038 A	04-03-1998
		JP 10507933 T	04-08-1998
WO 9708304 A	06-03-1997	IT RM950573 A	24-02-1997
		AU 6668696 A	19-03-1997
		CA 2228265 A	06-03-1997
		CN 1193997 A	23-09-1998
		EP 0846164 A	10-06-1998
		JP 10511556 T	10-11-1998